

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211988Orig1s000

SUMMARY REVIEW



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	May 12, 2021
From	Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD
NDA#	211988
Applicant	Heron Therapeutics, Inc.
Date of Original Submission and First Resubmission	October 30, 2018; Complete Response Letter Issued April 30, 2019 September 26, 2019; Complete Response Letter issued June 26, 2020
Date of Second Complete Response Submission	November 12, 2020
PDUFA Goal Date	May 12, 2021
Proprietary Name	Zynrelef™
Established or Proper Name	Bupivacaine and Meloxicam solution
Dosage Forms	Solution for soft tissue or periarticular instillation
Applicant Proposed Indication	(b) (4)
Applicant Proposed Dosing Regimens	Single dose administration for the following doses: – 400 mg bupivacaine and 12 mg meloxicam – 300 mg bupivacaine and 9 mg meloxicam – 200 mg bupivacaine and 6 mg meloxicam – 60 mg bupivacaine and 1.8 mg meloxicam
Regulatory Action	<i>Approval</i>
Approved Indication	For soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty. <u>Limitations of Use</u> Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spine and head and neck procedures.
Approved Dosing Regimens	Single-dose administration as follows: – For bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam. – For open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam. – For total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam. An additional dose of 200 mg/6 mg will be available for dosing flexibility for patients requiring less than the recommended 300 mg/9 mg or 400 mg/12 mg doses.

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CDTL=Cross-Discipline Team Leader

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

OPDP=Office of Prescription Drug Promotion

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OSE= Office of Surveillance and Epidemiology

OSI=Office of Scientific Investigations

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1. Benefit-Risk Assessment

This is the third review cycle for NDA 211988. The benefit:risk assessment has shifted from the two previous determinations, is now considered favorable, and supports approval of the drug product HTX-011, proposed tradename Zynrelef™, for postsurgical analgesia following bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty (TKA). The Applicant has adequately addressed the deficiencies discussed in the Complete Response Letter (CRL) issued on June 26, 2020. A detailed discussion of the previously identified nonclinical deficiencies and the Applicant's response is included in Section 4 of this review.

The following discussion is a brief summary of the information contained in the previously completed Cross-Discipline Team Leader (CDTL) and Division Director (DD) Summary Review by Drs. Renee Petit-Scott, Martha Van Clief, and Rigoberto Roca, CDTL Review by Dr. Martha Van Clief, and primary clinical review by Dr. Renee Petit-Scott.

HTX-011, developed by Heron Therapeutics, Inc (Heron), is a fixed-dose combination product composed of bupivacaine and meloxicam in a proprietary Biochronomer® vehicle to allow extended release of the drug product beyond that currently provided by administration of immediate-release bupivacaine. The proposed indication for HTX-011 is (b) (4)

(b) (4) The standard of care for most surgical procedures is the administration of local anesthetic medications via a variety of routes, including wound infiltration, peripheral nerve blocks, neuraxial blocks, and continuous infusion via indwelling peripheral nerve catheters. The limitation of the currently available local anesthetics is their relatively short duration of action and limited postsurgical analgesia.

The results of the HTX-011 drug development program support a statistically significant analgesic benefit over saline placebo and bupivacaine HCl wound infiltration for up to 72 hours post-operatively in two surgical models, unilateral bunionectomy, HTX-011 60 mg/1.8 mg evaluated in Study HTX-011-301 (301) and open unilateral inguinal herniorrhaphy, HTX-011 300 mg/9 mg evaluated in Study HTX-011-302 (302). Several opioid-related efficacy endpoints reached statistical significance as well, including proportion of patients who were opioid-free through 72 hours and reduction in overall opioid consumption. The results of Study HTX-011-209 (209), Cohort 2, a Phase 2b in patients undergoing TKA, also support the postsurgical analgesic benefit of HTX-011 compared to saline placebo. Because statistical significance was not reached in the comparison of HTX-011 to bupivacaine, in combination with lack of adequate nonclinical data to support the systemic safety of the maximum proposed dose of HTX-011, 400 mg/12 mg, Dr. Petit-Scott did not recommend approval of this dose during the initial review cycle. In the first NDA resubmission, dated September 26, 2019, however, Heron provided additional nonclinical data to support this highest proposed dose, and the pharmacology/toxicology and clinical pharmacology review teams concluded HTX-011 400 mg/12 mg could be approved for use in patients undergoing TKA based on this data. During the second review cycle, the Division recommended approval of all three doses of HTX-011 for the indicated procedures at such time as the additional nonclinical deficiencies were adequately addressed.

Subsequent to the first CRL, the Applicant conducted two additional open-label efficacy studies in patients undergoing bunionectomy [Study HTX-011-218 (218)] and in patients undergoing open inguinal herniorrhaphy [Study HTX-011-215 (215)]. The objectives of Study 218 were to evaluate individualized HTX-011 dosing and the impact of analgesic adjuncts on post-operative pain through 72 hours. The objective of Study 215 was to evaluate the impact of a multimodal analgesic regimen on post-operative pain through 72 hours. Because the studies were open-label and all treatment groups received HTX-011, definitive efficacy conclusions are challenging; however, in general, both studies appeared to demonstrate improved post-operative analgesia, either reduced mean pain intensity scores or larger proportion of patients who were opioid-free, compared to the results reported for the larger Phase 3 studies in the respective surgical populations.

During the second review cycle, the Division concluded that administration of HTX-011 60 mg/1.8 mg, 300 mg/9 mg, and 400 mg/12 mg were safe postsurgical analgesic treatments for patients undergoing bunionectomy, open inguinal herniorrhaphy, and TKA, respectively, at such time as the nonclinical deficiencies were adequately addressed. The adverse events of greatest concern associated with administration of HTX-011 are those due to local anesthetic systemic toxicity (LAST), particularly in patients who receive the highest HTX-011 doses, 300 mg/9 mg and 400 mg/12 mg, and local inflammatory and wound-related adverse events, particularly in patients undergoing bunionectomy. There did not appear to be a clinically significant increased incidence in potential LAST-related adverse events in patients treated with HTX-011 300 mg/9 mg compared to patients treated with saline placebo or bupivacaine HCl in Study 302, conducted in patients undergoing open inguinal herniorrhaphy. There were small, inconsistent differences across treatment groups. In the setting of concomitant administration of general anesthesia, however, causality determinations are challenging. A single patient in this study had a maximum plasma concentration ($C_{\max}$) greater than 1000 ng/mL (the concentration above which the Division generally considers the risk of LAST-related symptoms increased) at 24, 33, and 48 hours' post-operatively, but did not experience any LAST-related adverse events, including ECG changes, during those times.

In the three clinical studies which evaluated the highest proposed dose of HTX-011, 400 mg/12 mg, the pharmacokinetic (PK) results indicated there were patients with $C_{\max}$ values greater than 1000 ng/mL; however, it did not appear that these patients had an increased incidence of LAST-related adverse events compared to patients with $C_{\max}$ values less than 1000 ng/mL. In the study which evaluated patients undergoing bilateral augmentation mammoplasty, the highest mean $C_{\max}$ was reported of the three studies, 710 ng/mL. It is worth noting, however, that while the total dose of HTX-011 administered was 400 mg/12 mg, the dose was divided and administered sequentially, separated in time, to each breast pocket; therefore, the data may not truly represent a single administration of HTX-011 400 mg/12 mg, but divided sequential doses of 200 mg/6 mg. Additionally, augmentation mammoplasty is not an indicated procedure for administration of Zynrelef.

Regarding the risk of local inflammatory and wound-related adverse events, there did appear to be an increased incidence of wound-related adverse events primarily observed in patients undergoing bunionectomy in the Phase 3 study, 301, and the Phase 2a study, 208. The Division concluded, however, that HTX-011 could be approved for this indication for five reasons. First, the Division agreed with the Applicant that leakage of excess HTX-011 from the relatively small bunionectomy wound potentially contributed to the development of local inflammatory changes in the short-term (less than 42 days) by interrupting the approximation of wound edges, resulting in an increased risk of adverse events. The Division felt this risk could be adequately mitigated by language in the drug product label, advising clinicians to administer only as much HTX-011 as is necessary to coat the exposed tissues. Additionally, results from Study 218, discussed below, provide supportive information for this hypothesis. Second, the Division concluded that the majority of wound-related adverse events were mild, of relatively short duration, and resolved by the end of the study. Third, there were no reported cases of osteomyelitis in any patient who underwent a bunionectomy, suggesting that while there may be an increased incidence in local wound adverse events, they do not appear to result in adverse effects on the underlying bony structures. Of the low number of reported bony changes, such as malunion, there did not appear to be clinically meaningful differences between treatment groups. Fourth, because the conditions under which clinical studies are conducted may not represent standard clinical practice, it is possible that the surgical wounds may have been "over-graded" and reported as impaired healing. And lastly, the reported incidences of wound-related adverse events appeared to be consistent with reports in the published literature in patients undergoing bunionectomy. Regarding the safety profile of HTX-011 in soft tissue surgical models, there did not appear to be an increased incidence of clinically significant wound-related adverse events in patients undergoing inguinal herniorrhaphy, the only indicated soft tissue procedure.

The safety results from Study 218 and Study 215, described in detail in Section 8 of this review, support the favorable benefit:risk profile of HTX-011. Specifically, in Study 218, which evaluated individualized HTX-011

dosing up to 60 mg/1.8 mg in patients undergoing bunionectomy, instilled volumes ranging from 0.7 to 2.1 mL, there appeared to be a lower incidence of local inflammatory and wound-related adverse events when compared to the results reported for the Phase 3 study, 301. There were two patients each with wound drainage and dehiscence. The results from Study 215, conducted in patients undergoing open inguinal herniorrhaphy, are similar to those reported in the Phase 3 study, 302. While definitive safety conclusions based on data from open-label studies in which all treatment groups received HTX-011 are challenging, it is reassuring that the incidence of local inflammatory and wound-related adverse events was low and similar to or better than the results reported in the Phase 3 studies.

The risk of NSAID-related adverse cardiovascular and gastrointestinal (GI) events due to the meloxicam component of HTX-011 was discussed extensively during the first and second review cycles. Because the dose of NSAID medications at which there is no risk of related adverse events is unknown, the Division has required the inclusion of the NSAID boxed warning in all NSAID-containing products, including topical products. Therefore, while the systemic exposure to meloxicam was relatively low after instillation of the highest proposed HTX-011 dose, 400 mg/12 mg, the Division concluded that the boxed warning related to the risks associated with NSAID administration must be included in the final Zynrelef prescribing information. Of note, there did not appear to be any patient across clinical development who experienced either an adverse cardiovascular or GI event related to administration of HTX-011. In Study 218, additional oral NSAIDs were administered, and in Study 215, additional oral and i.v. NSAIDs were administered, and there did not appear to be an increased incidence in NSAID-related adverse events, albeit HTX-011 doses less than 400 mg/12 mg were evaluated.

In conclusion, the clinical benefits of HTX-011 administration during bunionectomy, open inguinal herniorrhaphy, and TKA outweigh the clinical risks discussed, and include a safe and novel route of administration, extended duration of postsurgical analgesia, and an additional analgesic treatment option. A main advantage of HTX-011 over other currently available bupivacaine products is the proposed route of administration, instillation, using a needle-less Luer lock syringe with a unique cone-shaped applicator. Because a needle is not used for administration, the risk of inadvertent intravascular administration and catastrophic LAST is minimized, thereby increasing the margin of safety of this bupivacaine-based product. Intravascular and systemic absorption is still a concern in the setting of large doses or administration in areas of increased vascularity; however, these concerns can be mitigated with clear language in the drug product label.

2. Background

This document will serve as the Cross-Discipline Team Leader (CDTL) and Division Director Summary review of new drug application (NDA) 211988 for the decision on regulatory action following resubmission on November 12, 2020.

NDA 211988 was initially submitted for approval through the 505(b)(2) regulatory pathway on October 30, 2018, for Zynrelef™, also referred to as HTX-011, a bupivacaine and meloxicam solution, indicated for the management of postsurgical pain. The Applicant, Heron Pharmaceuticals, Inc. (Heron), was relying on the Agency's previous findings of safety and efficacy for Marcaine™ (NDA 01964) and Mobic® (NDA 020938). Based on unresolved issues regarding device sterility, drug product quality, and nonclinical safety concerns, the application received a Complete Response Letter (CRL) on April 30, 2019. A Complete Response submission was received on September 26, 2019, and also received a CRL on June 26, 2020, based on the following unresolved nonclinical issues.

- Inadequate data to support the request for a waiver of reproductive and developmental studies for triacetin. While the Applicant concluded that the primary metabolites of triacetin do not represent a risk for reproductive and developmental effects, they provided no data to support the conclusion that triacetin instilled into a wound at the maximum daily dose will not result in systemic exposure to the triacetin molecule.
- Inadequate scientific bridge to the referenced oral reproductive and developmental studies submitted to qualify the safety of DMSO exposure via the proposed drug product. Instillation of the drug product may result in higher C_{max} and AUC compared to oral studies and, therefore, it is not clear if the referenced studies adequately address the safety of the proposed product.
- Inadequate data to support the proposed drug product specification (b) (4) at NMT (b) (4)%. The nonclinical and clinical lots tested to date do not contain this high of a percentage of (b) (4) and, therefore, do not qualify this specification. Further, there was inadequate data to support the conclusion that (b) (4) would not contribute to the local tissue effects of the drug product.
- The embryofetal development study in rabbits tested maleic acid via an oral route of administration rather than the proposed route of administration of the proposed drug product and there was an inadequate scientific bridge to support the conclusion that the study provides adequate characterization of the developmental effects of maleic acid exposures via installation into a wound.

Although not listed as a deficiency in the first cycle, the following comment was included in the second-cycle CRL.

- The proposed specification for DMSO of (b) (4) % has an upper limit that has never been tested in the Applicant's clinical or nonclinical development program. As DMSO may contribute to local tissue toxicity, the specification should be revised to reflect the testing completed, conduct a new study to characterize the local effects of the to-be-marketed drug product containing DMSO at the upper limit of proposed specification, or justify why DMSO at (b) (4) % will not contribute to the local tissue effects of the drug product.

The regulatory history and Applicant interactions following issuance of the second-cycle CRL are summarized in the following table.

Table 1. Key Regulatory History Subsequent to Issuance of Second-Cycle CR Letter

Meeting/Communication/Date	Event/Key Issues Identified
Complete Response Letter, June 26, 2020	Nonclinical deficiencies identified.
Proposed Amended Agreed iPSP and Request for Deferral, July 17, 2020	The Applicant submitted Amendment 2 to Amended iPSP, which proposed additional time for all studies, nonclinical and clinical, based on pending Division feedback from protocol amendments submitted in May 2020.
Type A End of Review Meeting, September 2, 2020	Purpose of the meeting was to obtain agreement on Heron's plan to address the nonclinical deficiencies in the CRL, and to gain agreement on whether the resubmission (b) (4). The Division did not agree that the nonclinical deficiencies could be addressed (b) (4). Additional discussion included the acceptability of the DMSO and maleic acid PK bridging data, evaluation of the safety of triacetin and its metabolites, and (b) (4) excipient assessments. The Division noted that there did appear to be adequate data to support approval of the highest recommended HTX-011 dose, 400 mg/12 mg; however, the final determination would be made during the review cycle.
Advice Letter, October 19, 2020	The Division provided the following advice regarding the proposed pediatric protocol changes. (b) (4)

Meeting/Communication/Date	Event/Key Issues Identified
	(b) (4)
NDA 211988 Resubmission, November 12, 2020	The Division determined the submission was a complete response and acceptable for review. A PDUFA goal date of May 12, 2021, was set.

3. Product Quality

There were no outstanding product quality issues identified during the second review cycle and the team recommended approval. During the current review cycle, the Applicant provided updated specifications, including limits for dimethyl sulfoxide (DMSO) and stability data.

The following information is adapted from the product quality reviews completed during this cycle.

Briefly, HTX-011 is a fixed-dose combination product consisting of bupivacaine, 29.25 mg/mL, and meloxicam, 0.88 mg/mL, indicated for administration into bunionectomy, open inguinal herniorrhaphy, and TKA wounds for postsurgical analgesia through 72 hours. As previously mentioned, the to-be-marketed presentations are as follows:

- Bupivacaine 400 mg + meloxicam 12 mg in 20 mL vial
- Bupivacaine 300 mg + meloxicam 9 mg in 20 mL vial
- Bupivacaine 200 mg + meloxicam 6 mg in 10 mL vial
- Bupivacaine 60 mg + meloxicam 1.8 mg in 10 mL vial

The proposed shelf-life is 36 months for the 400 mg/12 mg, 300 mg/9 mg, and 200 mg/6 mg presentations, and 24 months for the 60 mg/1.8 mg presentation.

In response to the additional non-clinical comment included in the second CRL regarding the proposed DMSO specification of (b) (4) %, a concentration not evaluated in either nonclinical or clinical studies, the Applicant tightened the DMSO acceptance criterion to (b) (4) % (the upper limit of which was evaluated in clinical studies). This specification is acceptable; however, there was concern (b) (4)

(b) (4) In response to an Information Request, the Applicant provided the following additional information.

The Applicant further stated that the in vitro release data for the lots met acceptance criteria. The product quality review team agrees with the Applicant's conclusion (b) (4)

The team further concluded that the stability data demonstrate (b) (4)

(b) (4) the rate of release is within specification. The biopharmaceutical reviewer concurred with this assessment.

The additional stability data provided by the Applicant during this review cycle indicated that that drug product batches tested at the long-term conditions were within the proposed acceptance criteria. The team did note that (b) (4)

all results were within specification.

The Division concurs with the conclusion of the product quality review team that there are no outstanding product quality issues that would prevent approval.

4. Nonclinical Pharmacology/Toxicology

The following discussion is adapted from the Pharmacology/Toxicology NDA Review and Evaluation completed by Dr. Jaime D'Agostino.

The drug product formulation contains several new excipients, defined by the FDA guidance document as excipients used at higher doses, concentrations, or routes of administration than previously approved drug products. Specifically, the proposed doses of AP135, DMSO, triacetin, and maleic acid exceeded levels present in FDA-approved drug products as per the CDER Inactive Ingredients Database (IID). In the initial NDA submission, adequate data were provided to characterize the reproductive and developmental safety profile of AP135 at the maximum recommended human dose (MRHD). However, the Applicant did not adequately justify the safety of DMSO, maleic acid, and triacetin with respect to the standard reproductive and developmental toxicology battery endpoints. In this second resubmission, the Applicant provided adequate pharmacokinetic bridging data and additional information from the published literature to support the safe levels of excipients in the drug product, demonstrating they are of minimal risk at the MRHD.

Regarding the local safety of HTX-011, the Applicant conducted two pivotal nonclinical studies, both 28-day repeat dose studies, in rat (Study 33-85) and dog (Study 33-86), where HTX-011 was administered via subcutaneous injection. These studies characterized the local toxicity, specifically a prolonged (up to 28 days) inflammatory response resembling a foreign body reaction, of the to-be-marketed formulation of HTX-011 at a margin of 1x. Results from studies in rats evaluating single doses (Study 33-48 and Study 33-55) suggest that the dermal effects were more severe, with some observations of necrosis, when compared to the multiple injections evaluated in the repeat-dose studies. These findings may be due to an increased injection volume used for the single injection compared to the volume used for multiple injections. This suspected relationship between increased injection volume and severity of local toxicity was also observed in a 28-day dog study. While definitive conclusions about injection volume and severity of local tissue effects are challenging, the pharmacology/toxicology review team concluded that increased amounts of locally applied HTX-011 does increase the risk for local tissue toxicity.

Results from a minipig study (Study 33-54) where HTX-011 was administered via wound instillation, demonstrated a minor impact on soft tissue wound healing, consistent with the findings from the clinical herniorrhaphy studies. It is worth noting, however, that the dose volumes normalized to the length of the incision were lower in the minipig study (1 mL/cm) than those evaluated in the clinical herniorrhaphy procedures (2.5-3.4 mL/cm).

Based on the totality of the nonclinical data, including local effects observed in animals treated with HTX-011 and the HTX-011 vehicle, it appears that local inflammatory changes are primarily due to the presence of the excipient tri(ethylene glycol)-based poly(orthoester) polymer (AP135) contained in the vehicle. Similar local effects were observed in studies using an APF18A polymer, which is (b) (4). There did not appear to be an adverse impact of HTX-011 administration on the integrity of evaluated surgical mesh or on wound healing. Additionally, there did not appear to be a meaningful delay in bone healing, based on findings from nonclinical bone healing and integrity evaluations.

Regarding systemic safety, results from the pivotal nonclinical studies demonstrated changes in measured hematology parameters, specifically an increase in reticulocytes. There were also increases in white blood cell, platelet, leukocyte, eosinophil, neutrophil, monocyte, and lymphocyte counts. Based on similar observations in animals treated with HTX-011 and the HTX-011 vehicle, the pharmacology/toxicology review team believes the observed changes in measured hematology parameters are likely due to exposure to systemically distributed breakdown fragments of the AP135 polymer. Similar to the local inflammatory effects, the hematology findings were also observed in studies evaluating an APF18A polymer, which is (b) (4) further supporting a role for AP135 in the observed hematology changes. Of note, the hematology changes were similar between the treatment and saline control groups following a two-week recovery period. Other systemic toxicities observed in the 28-day dog study included decreased activity, decreased body weight, and increased organ weights (liver, thymus, adrenal, and kidney). Because these findings were not observed after single-dose exposure, they are unlikely to be clinically relevant.

Regarding the mechanism of action of HTX-011, the Applicant has stated (b) (4)

(b) (4)

As noted in the CDTL/DD Summary Review completed during the second review cycle, the Applicant provided adequate nonclinical support for the highest proposed dose of HTX-011, 400 mg/12 mg. Briefly, the Applicant conducted an additional 14-day study in rats using HTX

formulations containing only bupivacaine (not the to-be-marketed formulation) at higher doses than evaluated in a previous rat study. The toxicological findings in this study were similar to the results from the 28-day studies, which included an inflammatory response consistent with a foreign body reaction and changes in measured hematology parameters. Due to differences in dosing volumes, formulations, and durations of treatment, it is difficult to determine whether the magnitude of the changes was more severe in this study compared to previous studies which used lower doses of bupivacaine. The bupivacaine systemic exposure (AUC_{inf}) in this study (52,900 ng·h/mL) was higher than the highest reported bupivacaine exposure in the Applicant's clinical studies (Study 209, total knee arthroplasty, 31,173 h·ng/mL) by a factor of ~1.7x. While the AUC_{inf} was not calculated in the 28-day dog study, the study did provide data in a second species that had similar bupivacaine exposure over 24 hours as humans exposed to 400 mg bupivacaine (~1x). The single systemic finding in dogs at this exposure level was an increase in reticulocytes. Based on these results, the pharmacology/toxicology team concluded, and the clinical pharmacology review team agreed, that the Applicant had provided adequate support for the safety of the 400 mg dose of bupivacaine in the highest proposed HTX-011 dose. The team did comment that they defer to the clinical team regarding the relevance of the observed changes in hematology parameters.

The Applicant conducted multiple extraction and leachable studies to characterize the safety of the container closure system, and the deficiencies identified during the initial review cycle were adequately addressed in the first complete response NDA submission. The Applicant provided a detailed risk assessment for the leachables and permissible daily exposures (PDEs) were derived for the compounds based on available data. The maximum detected levels of the leachables were all below the calculated PDEs and are not anticipated to be a safety concern. The deficiency related to the drug product (b) (4) was addressed in this resubmission (b) (4)

Refer to Section 3 of this review for additional information regarding the proposed DMSO acceptance criteria.

The pharmacology/toxicology review team has concluded, and we concur, that the Applicant has adequately addressed the nonclinical deficiencies identified in the previous submissions, and there are no outstanding nonclinical concerns that would preclude approval of HTX-011 60 mg/1.8 mg, 300 mg/9 mg, and 400 mg/12 mg for use during bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty, respectively. The nonclinical data do suggest a local inflammatory response after administration of HTX-011 at clinically relevant doses. We believe, however, that local inflammatory and wound-related adverse events were primarily observed in patients undergoing bunionectomy, limited to the soft tissue, and can be mitigated with information in the drug product label. Regarding the observed changes in hematology parameters in the nonclinical studies, there were changes observed in the clinical studies; however, they were reported across all treatment groups and there did not appear to be clinically meaningful differences in patients treated with HTX-011.

5. Clinical Pharmacology

No additional clinical pharmacology data were submitted in support of this application that would impact the previous conclusion regarding the safety and efficacy of the highest proposed HTX-011 dose, 400 mg/12 mg. The review team concluded during the second review cycle that adequate data were provided to support the systemic safety of HTX-011 400 mg/12 mg, and that at such time as the identified nonclinical deficiencies were adequately addressed, would recommend approval.

Refer to the clinical pharmacology review completed by Dr. Suresh Narahariseti for additional information regarding the PK profile of all proposed doses of HTX-011.

6. Clinical Microbiology

HTX-011 is not a therapeutic antimicrobial, therefore clinical microbiology data were neither required nor submitted.

7. Clinical/Statistical - Efficacy

During the previous review cycle, review of the first complete response submission, the Division concluded that the Applicant had demonstrated substantial evidence of efficacy and recommended approval of HTX-011 60 mg/1.8 mg, 300 mg/9 mg, and 400 mg/12 mg for administration during unilateral bunionectomy, unilateral open inguinal herniorrhaphy, and unilateral total knee arthroplasty (TKA), respectively, at such time as the identified nonclinical deficiencies were adequately addressed. Refer to the Cross-Discipline Team Leader and Division Director Summary Review completed by Drs. Petit-Scott, Van Clief, and Roca on June 26, 2020, for additional information regarding the efficacy conclusions. Subsequent to the first complete response submission, the Applicant completed two additional open-label efficacy studies, which will be briefly discussed here. There are three on-going studies (b) (4)

Refer to the following table for a summary of all studies completed subsequent to the first review cycle, or pending or on-going at the time of completion of this summary review.

Study	Population	Status
BUPI 501 (PK)	IHR; tx groups Exparel 266 mg and bupiv 300 mg continuous wound infusion over 60h; Open-label	Complete
BUPI 502 (PK)	Augmentation mammoplasty evaluating two different routes of bupiv. admin.; Open-label	Complete
HTX-011-215	IHR with MMA; Open-label	Complete
HTX-011-218	Bunionectomy with individualized dosing and MMA; Open-label	Complete
(b) (4)		On-going

	(b) (4)	Pending
		On-going
		On-going
IHR: inguinal hernia repair (herniorrhaphy); MMA: multimodal analgesia		(b) (4)

Study HTX-011-218 (218) was an open-label efficacy (and safety) study conducted in 78 patients undergoing bunionectomy who received a single individualized dose of HTX-011, up to 60 mg/1.8 mg. As discussed in detail in Section 8 of this review, there was concern noted in the earlier bunionectomy studies [Phase 3 Study HTX-011-301(301) and Phase 2 Study HTX-011-C2016-208 (208)] that excess HTX-011 may have been leaking out of the surgical wound, thereby impeding timely approximation of the wound edges, resulting in the development of local inflammatory and wound-related adverse events. The Applicant felt that an individualized dose to only cover the exposed wound, as opposed to administration of the entire dose, would result in less leakage and potentially mitigate the risk of local inflammatory and wound-related adverse events. In Study 218, patients in Cohort 1 (30) received a single individualized dose of HTX-011, Cohort 2 (17) received a single individualized dose of HTX-011 and three doses of oral aprepitant through 48 hours’ post-operatively, and Cohort 3 (31) received a single individualized dose of HTX-011 with scheduled alternating ibuprofen and acetaminophen post-operatively. The primary efficacy endpoint was the mean pain intensity with activity through 72 hours’ post-operatively. In general, it did appear that the mean pain intensity with activity scores through 72 hours in all three cohorts were lower compared to those in the Phase 3 study (Study 301); however, because this was an open-label study, the efficacy results are difficult to interpret and definitive conclusions about cross-study comparative results cannot be made.

Study HTX-011-215 (215) was an open-label safety and efficacy study conducted in 63 patients undergoing open inguinal herniorrhaphy using a multimodal analgesic regimen. Patients in Cohort 1 (33) received HTX-011 300 mg/9 mg with alternating doses of ibuprofen and acetaminophen post-operatively, and patients in Cohort 2 (30) received the same regimen in addition to one dose of intravenous (i.v.) ketorolac intra-operatively. The primary efficacy endpoint was proportion of patients opioid-free through 72 hours’ post-operatively. It appears that both cohorts demonstrated an analgesic benefit with the multimodal regimen, and the proportion of opioid-free patients through 72 hours was reportedly higher than that observed in the Phase 3 study in the same surgical population (Study 302). This was an open-label study, such that the efficacy results are difficult to interpret and definitive conclusions about cross-study comparative results cannot be made; however, it is not surprising that scheduled non-opioid analgesia around the clock through 72 hours resulted in less mean opioid use and a higher proportion of patients who required no opioid analgesia.

(b) (4)

(b) (4)

In conclusion, we recommend approval of HTX-011 60 mg/1.8 mg, 300 mg/9 mg, and 400 mg/12 mg for administration during bunionectomy, open inguinal herniorrhaphy, and TKA, respectively. An additional dose of 200 mg/6 mg will be available for dosing flexibility for patients requiring less than the recommended 300 mg/9 mg or 400 mg/12 mg doses. Refer to the primary clinical review completed by Dr. Petit-Scott and the CDTL/DD Summary Review completed by Drs. Van Clief and Roca during the first review cycle, and the CDTL/DD Summary Review completed by Drs. Petit-Scott, Van Clief, and Roca during the second review cycle for additional information.

8. Safety

During the second review cycle, the Division concluded that administration of HTX-011 60 mg/1.8 mg, 300 mg/9 mg, and 400 mg/12 mg were safe postsurgical analgesic treatments for patients undergoing unilateral bunionectomy, unilateral open inguinal herniorrhaphy, and unilateral TKA, respectively, at such time as the identified nonclinical deficiencies were adequately addressed.

The adverse events of greatest concern associated with administration of HTX-011 are those due to local anesthetic systemic toxicity (LAST), particularly in patients who receive the highest HTX-011 doses, 300 mg/9 mg and 400 mg/12 mg, and local inflammatory and wound-related adverse events, particularly in patients undergoing bunionectomy. The following discussion will summarize these adverse events reported during the previous review cycles, as well as from the completed open-label studies; NSAID-related cardiovascular and gastrointestinal (GI) adverse events; and information from the safety update.

LAST-Related Adverse Events

In her primary clinical review, completed during the initial review cycle, Dr. Petit-Scott concluded there did not appear to be a clinically significant increased incidence in potential LAST-related adverse events in patients treated with HTX-011 300 mg/9 mg undergoing open inguinal herniorrhaphy, or in patients treated with HTX-011 400 mg/12 mg undergoing TKA, bilateral augmentation mammoplasty, or abdominoplasty, compared to patients treated with saline placebo or bupivacaine HCl. She felt that the small and inconsistent differences across treatment groups were not clinically meaningful, particularly in the setting of concomitant administration of general anesthesia, which makes detection of LAST and determination of causality challenging.

Of the three Phase 2 studies which evaluated HTX-011 400 mg/12 mg, patients undergoing TKA in Study 209 had the highest individual C_{max} values reported. Specifically, there were 10 patients with C_{max} values greater than 1000 ng/mL (the concentration above which the Division generally believes the risk of LAST increases) and 6 had time of maximum concentration (T_{max}) later than 24 hours' post-operatively. Dr. Petit-Scott concluded there did not appear to be an increased incidence in LAST-related adverse events in these patients compared to patients with C_{max} values less than 1000 ng/mL. In Study HTX-011-211 (211), conducted in patients undergoing bilateral augmentation mammoplasty, the highest mean C_{max} value was reported, 710 ng/mL, and there were five patients with C_{max} values greater than 1000 ng/mL, with the latest reported T_{max} 5.98 hours. There did not appear to be an increased incidence of LAST-related adverse events reported for these patients. There did appear to be an overall increased incidence of the LAST-related adverse events of hypotension, dysgeusia, and bradycardia in HTX-011-treated patients compared to those treated with saline placebo or bupivacaine HCl in this study. It is worth noting, however, that the highest incidence of LAST-related adverse events was reported in the exploratory HTX-011 240 mg/7.2 mg treatment group, and not the HTX-011 400 mg/12 mg treatment group. Additionally, while the total dose of HTX-011 administered in Study 211 was 400 mg/12 mg, the dose was divided and administered sequentially, separated in time, to each breast pocket; therefore, the data may not truly represent a single administration of HTX-011 400 mg/12 mg, but divided sequential doses of 200 mg/6 mg. In Study HTX-011-C2015-203 (203), conducted in patients undergoing complete abdominoplasty, there were no reported C_{max} values greater than 1000 ng/mL.

In the on-going study in patients undergoing TKA (Study 306), there were five patients with C_{max} values greater than 1000 ng/mL reported in the Safety Update. Two patients experienced hypotension without other potential LAST-related adverse events and the other three patients did not report any potential LAST-related adverse events. For those patients who experienced potential LAST-related adverse events, the C_{max} values were less than 1000 ng/mL.

There were no patients in any study who received HTX-011 400 mg/12 mg with $C_{\max}$ values greater than 2000 ng/mL, the concentration reported in the published literature above which the risk of LAST increases, at any measured time point. Based on the totality of the safety and PK data, the overall risk of development of LAST due to administration of the three doses of HTX-011 is low and does not adversely impact the benefit:risk assessment for this product.

Local Inflammatory and Wound-Related Adverse Events

Regarding the risk of local inflammatory and wound-related adverse events, there did appear to be an increased incidence of wound-related adverse events primarily observed in patients undergoing bunionectomy in the Phase 3 study, 301, and the Phase 2a study, 208. However, the Division concluded, during the previous review cycles, that HTX-011 could be approved for this indication, for five reasons. First, the Division agreed with the Applicant that leakage of excess HTX-011 from the relatively small bunionectomy wound potentially contributed to the development of local inflammatory changes in the short-term (less than 42 days) by interrupting the approximation of wound edges, resulting in an increased risk of adverse events. The Division felt this risk could be adequately mitigated by language in the drug product label, advising clinicians to administer only as much HTX-011 as is necessary to coat the exposed tissues. Second, the Division concluded that the majority of wound-related adverse events were mild, of relatively short duration, and resolved by the end of the study. Third, there were no reported cases of osteomyelitis in any patient who underwent a bunionectomy, suggesting that while there may be an increased incidence in short-term soft tissue adverse events, they do not appear to result in adverse effects on the underlying bony structures. Of the low number of reported bony changes, such as malunion, there did not appear to be clinically meaningful differences between treatment groups and several cases were associated with trauma (e.g., stubbed operative toe). Fourth, because the conditions under which clinical studies are conducted may not represent standard clinical practice, it is possible that the surgical wounds may have been “over-graded” and reported as impaired healing. And lastly, the reported incidences of wound-related adverse events appeared to be consistent with reports in the published literature in patients undergoing bunionectomy.

Regarding the safety profile of HTX-011 in soft tissue surgical models, there did not appear to be an increased incidence of clinically significant wound-related adverse events in patients undergoing inguinal herniorrhaphy, the only indicated soft tissue surgical procedure. In Study 203, conducted in patients undergoing complete abdominoplasty, there was an increased incidence of wound dehiscence in patients treated with HTX-011 300 mg/9 mg administered via a combination of injection and instillation, which may have been due to disruption of the posterior rectus plication and umbilicus repositioning. The risk of this adverse event can be mitigated by language in the drug product label, including limited indicated surgical procedures and route of administration, instillation, not injection or infiltration.

As discussed in Section 7 of this review, there have been two additional, open-label clinical studies completed subsequent to the first CRL, one in patients undergoing bunionectomy (Study 218) and one in patients undergoing open inguinal herniorrhaphy (Study 215). As previously mentioned, it is believed that leakage of excess HTX-011 may contribute to the development of wound-related adverse events in patients undergoing bunionectomy; therefore,

Study 218 was conducted to evaluate the safety (and efficacy) of individualized dosing in this surgical population. Investigators in this study were advised to apply only as much HTX-011 as was necessary to “coat the pain-generating tissues ensuring there was not an excess that could be expressed from the site during closure”. The volume of HTX-011 administered ranged from 0.7 to 2.1 mL, the maximum recommended volume. Because this was an open-label study, there was no comparator treatment group, and the total number of evaluated patients was low (78), definitive safety conclusions are challenging; however, there did appear to be a lower incidence in local inflammatory adverse events (approximately 4% overall, three patients total) in this study compared to those reported in Study 301 (approximately 29%). Regarding abnormal wound healing assessments, there appeared to be a lower incidence in this study (approximately 74%) compared to Study 301 (approximately 81%), with bruising, edema, and erythema most commonly reported.

There was a higher incidence of wound drainage and dehiscence in Study 218 compared to Study 301. In response to an Information Request, the Applicant clarified that two patients had serosanguinous wound drainage; one was prophylactically treated with oral antibiotics and the other received no treatment. Of the two patients who developed wound dehiscence, one patient had the serious adverse events (SAEs) of abscess and cellulitis and underwent incision and drainage of the wound (described below), and one had “very minor” wound separation requiring no treatment.

The patient with the SAEs of abscess and cellulitis in Study 218 had a prior history of coronary artery disease and stent insertion on clopidogrel, and methicillin-resistant staphylococcus aureus (MRSA) on the head. She developed a hematoma on Day 20, and the SAEs of abscess and cellulitis on Day 25. These SAEs required incision, drainage, debridement, and antibiotic administration, and resolved on Day 31. Wound cultures were positive for MRSA infection. The adverse events reported for this patient may possibly have been related to study drug administration; however, she also had several risk factors for post-operative wound infection, including early resumption of antiplatelet therapy and history of MRSA infection.

The results from Study 215, conducted in patients undergoing open inguinal herniorrhaphy, are similar to those reported in Study 302, and it does not appear that administration of HTX-011 300 mg/9 mg increased the risk of development of local inflammatory or wound-related adverse events. Specifically, the overall incidence of local inflammatory adverse events reported in Study 215 was approximately 2%, compared to approximately 4% in Study, 302. While definitive safety conclusions based on data from Study 215, an open-label study where all treatment groups received HTX-011, are challenging, it is reassuring that the reported local inflammatory and wound-related adverse events occurred with similar frequency as that observed in the larger Phase 3 study.

An Additional Safety Issue

In contrast to the findings reported in Dr. D’Agostino’s pharmacology/toxicology review, there were no consistent or clinically meaningful changes in measured hematology parameters in patients treated with HTX-011 compared to patients treated with saline placebo or different doses of bupivacaine HCl. The changes that were observed may have been related to the

surgical procedure performed and not the dose of HTX-011 administered. Additionally, there were no clinically meaningful differences between treatment groups at the last laboratory assessment, generally Day 10. An in-depth review of white blood cell counts in patients treated in the Phase 3 studies, Study 301 and Study 302, was performed by Dr. Petit-Scott during the initial review cycle given the concerns surrounding wound-related adverse events, and she did not identify clinically meaningful differences between treatment groups. Refer to her primary clinical review for additional information regarding changes in measured laboratory parameters in the clinical studies.

NSAID-Related Cardiovascular and GI Adverse Events

The risk of NSAID-related adverse cardiovascular and gastrointestinal (GI) events due to the meloxicam component of HTX-011 was discussed extensively during the first and second review cycles. Because the dose of NSAID medications at which there is no risk of related adverse events is unknown, the Division has required the inclusion of the NSAID boxed warning in the prescribing information of all NSAID-containing products, including topical products. Therefore, while the systemic exposure to meloxicam was relatively low after instillation of the highest proposed HTX-011 dose, 400 mg/12 mg, the Division concluded that the boxed warning related to the risks associated with NSAID administration must be included in the final prescribing information. Of note, there did not appear to be any patient across clinical development who experienced either an adverse cardiovascular or GI event related to administration of HTX-011. In Study 218, additional oral NSAIDs were administered, and in Study 215, additional oral and i.v. NSAIDs were administered, and there did not appear to be an increased incidence in NSAID-related adverse events, albeit HTX-011 doses less than 400 mg/12 mg were evaluated.

Information from the Safety Update

The safety update included information from the three on-going studies, conducted in patients undergoing open inguinal herniorrhaphy (Study 304), TKA (Study 306), and caesarean delivery (Study 220). All three studies included treatment groups evaluating multimodal analgesia, which involved administration of additional NSAIDs for several days post-operatively.

There was a single patient in Study 304 who reportedly had the SAE of peptic ulcer hemorrhage requiring hospitalization, and a single patient in Study 306 who had the SAE of gastritis requiring hospitalization. There was also a patient treated in Study in 306 who experienced haematemesis (*sic*). While these adverse GI events may have been related to administration of meloxicam in HTX-011, it is more likely that the additional NSAID medication included in the multimodal analgesic regimens, and aspirin for deep venous thrombosis prevention in Study 306, contributed to the development of NSAID-related GI adverse events. There did not appear to be an increased incidence in cardiovascular-related adverse events in patients who received additional NSAID medication compared to those who did not in the previously completed Phase 2 and 3 studies. Evaluation of the safety data at the conclusion of the ongoing multimodal analgesic regimen studies will inform the possible risks associated with HTX-011 and additional NSAID administration; however, because these three studies are open-label without non-HTX-011 comparator treatment groups, definitive conclusions will be challenging.

There did not appear to be clinically significant local inflammatory or wound-related adverse events reported in the three on-going studies. Of the events reported to date, all resolved at the time of the last follow-up assessment without long-term sequelae.

In conclusion, the clinical benefits of HTX-011 administration during bunionectomy, open inguinal herniorrhaphy with mesh, and TKA outweigh the clinical risks discussed. A main advantage of HTX-011 over other currently available bupivacaine products is the proposed route of administration, instillation, using a needle-less Luer lock syringe and a unique cone-shaped applicator. Because a needle is not used for administration, the risk of inadvertent intravascular administration and catastrophic LAST is minimal, thereby increasing the margin of safety for this bupivacaine-containing product. Increased intravascular and systemic absorption are still possible in the setting of large doses or administration in areas of increased vascularity; however, these can be mitigated with clear language in the prescribing information.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The safety and efficacy of HTX-011 has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. An amended iPSP was submitted on July 19, 2019, with revised dates. The amended iPSP was agreed to on October 11, 2019.

A draft protocol for Study HTX-011-216 was submitted on September 11, 2018, which proposed to evaluate the safety, efficacy, and pharmacokinetic profiles of HTX-011 in pediatric patients 3 to less than 17 years of age. The draft protocol was reviewed, comments provided to the Applicant, and the final study protocol was submitted on December 28, 2018. On May 8, 2020, the Applicant submitted revised clinical (and nonclinical) study timelines

202 [REDACTED] (b) (4)
Protocol Version 2.1 for Study HXT-011-216, was submitted on May 20, [REDACTED] (b) (4)

There were several communications with the Applicant [REDACTED] (b) (4)

As discussed in Section 13 of this review, four post-marketing requirements will be issued; two nonclinical PMRs for juvenile animal studies, and two clinical PMRs for two age groups, birth to less than three years of age and three to less than 17 years of age. Based on concerns surrounding the risk of renal toxicity with NSAID administration in children less than one year of age, consideration will be given for a waiver request for this age group based on any concerning safety signals identified in older pediatric patients or in the juvenile animal studies.

Refer to Section 13, Decision/Action/Benefit/Risk Assessment for information regarding the pediatric post-marketing requirements issued with the approval action.

11. Other Relevant Regulatory Issues

There are two other relevant regulatory issues that needed to be addressed during this review cycle; clarification of the Applicant's clinical development program to satisfy the requirements described in 21 CFR 300.50 for fixed-combination drugs, and the Consultation Response on the citizen petition submitted by Pacira Pharmaceuticals, Inc. (Pacira).

The Applicant's clinical development program to satisfy the requirements described in 21 CFR 300.50 for fixed-combination drugs

Under 21 CFR 300.50(a)(1), "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." Fixed-combination drugs are intended to provide greater effectiveness than either ingredient alone, either by having a greater effect for a single indication or by having an active ingredient enhance the safety or effectiveness of another active ingredient. Factorial studies should demonstrate the contribution of each component in the fixed-combination drug. Bupivacaine and low-dose meloxicam are the active pharmaceutical ingredients (APIs) in HTX-011. There is no mention in 21 CFR 300.50 indicating that the components must be studied in the same or similar formulation as the to-be-approved fixed-combination drug, nor that each proposed dose needs to be studied using the factorial study design.

The Applicant conducted two Phase 2 factorial studies, Study 202 in patients undergoing inguinal hernia repair and Study 208 in patients undergoing bunionectomy, to assess the contribution of each drug component, bupivacaine and low-dose meloxicam, to the activity of the fixed-combination drug. The following five treatment groups were evaluated in each study:

- HTX-011 (referred to as HTX-011-056 in these studies): the to-be-marketed bupivacaine and meloxicam formulation, which includes different doses of each component in the Biochronomer vehicle
- HTX-002: the bupivacaine component in the same Biochronomer vehicle as the to-be-marketed formulation
- HTX-009: the meloxicam component in the same Biochronomer vehicle as the to-be-marketed formulation
- Bupivacaine HCl 0.5%
- Placebo: normal saline

The results from Study 202 and Study 208 indicate that HTX-011 is categorized as a combination in which one active ingredient is intended to provide a direct effect that enhances the safety or effectiveness of another active ingredient.¹ Specifically, the meloxicam alone formulation (HTX-009) was undifferentiated from placebo, supporting the Applicant's conclusion that there is one disease-active component, bupivacaine, in HTX-011. The proportion of bupivacaine and meloxicam evaluated in the factorial studies is consistent across all doses evaluated in subsequent Phase 2 and Phase 3 clinical studies, such that all HTX-011 doses which demonstrate adequate safety and efficacy and maintain this same proportion of active ingredients can be approved.

During preparation of the Consultation Response (discussed below), we identified a sentence, on page 18, in the End-of-Phase 2 meeting minutes that was ambiguous and potentially subject to multiple interpretations. The sentence in the Discussion section for Question 8, which is in regards to the acceptability of the proposed primary efficacy endpoint in the Phase 3 studies, states the following, "The Division stated that based on the combination rule (CFR 300.50) they will need to demonstrate superiority versus placebo and bupivacaine and that the combination rule applies." This statement could be interpreted to mean the Sponsor is required to demonstrate their product's superiority over bupivacaine IR, an active control generally administered via wound infiltration, in their confirmatory efficacy studies for approval of the marketing application. This, however, is not required, because confirmatory efficacy studies upon which, in part, approvals are based do not need to demonstrate superiority over an active control. The next sentence on the same page of the meeting minutes states the following, "The Division explained that the Sponsor would need to demonstrate reproducible results in their studies to claim superiority over the active control." This statement refers to the data that would be needed to support a comparative claim, over the active control, in this case bupivacaine IR administered via wound infiltration, in the product label and is accurate. To assess the contribution of each drug component in HTX-011 and meet the requirements of 21 CFR 300.50, Heron conducted two factorial studies, Study 202 and 208, which demonstrated that bupivacaine in the Biochronomer vehicle (designated HTX-002) is the disease-active ingredient.

Consultation Response on the Citizen Petition submitted by Pacira Pharmaceuticals, Inc. (Pacira)

On July 25, 2018, the Office of Regulatory Policy (ORP) requested a consult on a citizen petition (FDA-2018-P-1780) submitted by Pacira dated May 7, 2018. Pacira is the NDA holder for Exparel®. The subject of Parica's citizen petition is the development of HTX-011. Pacira

¹ On December 23, 2015, the Agency issued a Proposed Rule to revise the requirements of 21 CFR 300.50, and described four categories of fixed-combination drugs:

- Combinations in which individual active ingredients are directed at the same sign, symptom, or condition
- Combinations in which one active ingredient is intended to provide a direct effect that enhances the safety or effectiveness of another active ingredient
- Combinations in which active ingredients are directed at different signs or symptoms of a disease or condition
- Combinations in which active ingredients are directed at different diseases or conditions

lists multiple concerns regarding Heron's HTX-011 in the petition, including concerns that Heron must demonstrate that a proposed fixed-combination of bupivacaine and meloxicam satisfies the safety and efficacy requirements of the Combination Rule, and concerns regarding inclusion of a boxed warning in HTX-011 labeling due to safety concerns associated with meloxicam administration, as well as, additional concerns regarding the safety associated with the use of Heron's proprietary, extended-release delivery technology, the Biochronomer and its inactive ingredients. Pacira's petition requested that FDA take the following actions:

- Refrain from approving any NDA for a fixed-combination of bupivacaine and meloxicam unless the NDA includes sufficient evidence from adequate and well-controlled studies, including factorial studies that compare the combination of bupivacaine and meloxicam to each of the component drugs alone.
- Refrain from approving any NDA for bupivacaine-meloxicam combination delivered in a novel ER vehicle unless the safety concerns posed by such a combination are adequately addressed, including in a boxed warning for the NSAID component of the proposed product.

ORP's consult requested that DAAP address all the issues raised in Pacira's petition. In particular, ORP requested that DAAP provide detailed answers to the following questions (abbreviated):

- 1) Do you agree with the Petitioner's view that factorial studies are needed in the two circumstances described immediately above?
- 2) The petitioner asserts that FDA has required factorial studies to support the approval of combination products intended to treat pain, particularly where each active ingredient in the combination is directed at the same sign or symptom of the disease or condition. (See Petition at 5,8). Do you agree that bupivacaine and meloxicam in HTX-011 are both intended to treat pain and that factorial studies would be needed for that reason to support its approval?
- 3) Do you agree with the Petitioner that meloxicam may affect the safety and effectiveness of bupivacaine when modified by Heron's Biochronomer technology and that factorial studies are needed for this reason as well?
- 4) Please explain whether or not you agree with Petitioner's assertion that NSAIDs should be used with caution in postsurgical settings. (Petition at 7). In responding to this request, address Petitioner's contentions that NSAIDs have negative effects on wound healing (such as through NSAIDs' antiproliferative effect on blood vessels and skin), decrease the granulocytic inflammatory reaction, and are associated with anaphylactic reactions and increasing scar formation. (Petition at 7).
- 5) Please explain whether you agree with Petitioner's assertion that HTX-011 poses significant cardiovascular risks. (Petition at 9). Discuss whether you agree that the labeling for HTX- 011 should include a boxed warning to address safety concerns associated with the drug's NSAID component. In your response, please address Petitioner's assertions that: (a) single-administration use may be associated with potential cardiovascular events; and (b) there is no evidence that the risks are significantly lower for locally administered products compared to systemically delivered NSAIDs. (Id.)
- 6) Please explain what Phase III pivotal study/studies Heron has submitted in support of this NDA.

Detailed responses to the posed questions are included in our Consultation Response. In summary, we conclude that the data submitted by Heron in NDA 211988 is sufficient to characterize the safety and to establish substantial evidence of effectiveness of HTX-011. Furthermore, the requirements of 21 CFR 300.50 for fixed-combination drugs have been adequately addressed with results from the two Phase 2 factorial studies conducted by Heron.

Refer to Dr. Petit-Scott's primary clinical review, dated April 30, 2019, for a discussion regarding financial disclosures and clinical site inspections for the completed clinical studies.

12. Labeling

During labeling negotiations, there were three main areas of disagreement; limited surgical indication, inclusion of opioid use information, and the need for inclusion of all NSAID template safety language, including drug interactions.

Regarding the limited surgical indication, the Applicant proposed an amended indication, (b) (4). We disagreed with this proposal for the following reasons (summarized):

(b) (4)

Regarding inclusion of opioid use information, the Applicant initially proposed (b) (4). During labeling negotiations, we conveyed

to the Applicant

(b) (4)

The Applicant was initially reluctant to include all NSAID safety template language, but agreement was reached during the second round of labeling negotiations.

The Applicant proposed including ‘extended-release’ in the product title and in different sections throughout the label. For a local anesthetic drug product to include ‘extended-release’, it must demonstrate a longer duration of effect when compared to immediate-release local anesthetics, in this case immediate-release bupivacaine, in addition to an extended-release PK profile. Because Zynrelef did demonstrate a statistically significant longer duration of effect compared to immediate-release bupivacaine in Studies 301 and 302, and a clinically meaningful trend in that direction in Study 209, the Division agrees that Zynrelef is an extended-release bupivacaine product, and that language is acceptable in the prescribing information.

The following is a high-level summary of edits made to the final prescribing information.

- **INDICATIONS AND USAGE:**

Information in this section should include only that required to clearly convey the use(s) of the drug for which it has been shown to be safe and effective; therefore, the approved indications include three evaluated surgical procedures; bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty. The proposed language

(b) (4)

was deleted.

The following Limitations of Use statement was included in the final label, based on concerns regarding the use of Zynrelef in surgical procedures for which there is a lack of safety data.

Limitations of Use

Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spine, and head and neck procedures.

- **DOSAGE AND ADMINISTRATION:**

Edits to this section were intended to clarify the risks associated with bupivacaine administration, required personnel and equipment during Zynrelef administration, and to

clarify the risks of additional local anesthetic and NSAID administration. The preparation and administration instructions were organized in a more concise manner, and dosing specific to the three surgical indications was included.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
The following boxed warning regarding the risks associated with NSAID administration was included in the final label:

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND
GASTROINTESTINAL EVENTS**

See full prescribing information for complete boxed warning.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)
- ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)

The Division requested the Applicant include safety information in Section 6 regarding the increased incidence of local inflammatory adverse reactions and changes in bone healing in patients treated with Zynrelef undergoing bunionectomy. Additional safety information regarding administration of bupivacaine was included based on the recently (August, 2020) updated Marcaine label.

- CLINICAL STUDIES:
Edits made to this section were intended to clarify the clinical studies upon which the approval for use in three surgical procedures was based. The efficacy results are described in the text of this section in addition to figures depicting mean pain intensity scores, with activity for bunionectomy and inguinal herniorrhaphy, and at rest for TKA, over 72 hours. Because Zynrelef demonstrated an analgesic benefit over immediate-release bupivacaine in all three clinical studies, the Division included opioid use-related secondary efficacy endpoint results in this section. Specifically, results describing proportion of patients opioid-free for all three studies, and median total opioid consumption for Study 302 were included to provide additional pertinent prescribing information for the clinician.

Consultations were obtained from the Division of Medication Error Prevention and Analysis (DMEPA) during the current and previous review cycles, and the Division of Pediatric and Maternal Health (DPMH) during the initial review cycle. Their recommendations were considered and incorporated into the label.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action

Approval.

Benefit:Risk Assessment:

As noted above, the Applicant has adequately addressed the deficiencies discussed in the Complete Response Letter issued on June 26, 2020, the benefit:risk assessment is favorable, and the application is approvable.

Post-Marketing Requirements (PMRs)

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing. The clinical pediatric PMRs and the study goals for this application are as follows:

- Conduct a multicenter study to evaluate the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients 3 to less than 17 years of age undergoing unilateral open inguinal herniorrhaphy.

The goal of this study is to evaluate the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients 3 to less than 17 years of age undergoing unilateral open inguinal herniorrhaphy.

- Conduct a multicenter study to assess the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric patients from birth to less than 3 years of age undergoing unilateral open inguinal herniorrhaphy.

The goal of this study is to assess the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric patients from birth to less than 3 years of age undergoing unilateral open inguinal herniorrhaphy.

The nonclinical PMRs are as follows:

- Conduct a juvenile animal study in the rodent model to characterize the impact of DMSO on the developing brain to support clinical studies in pediatric patients under three years of age.
- Conduct a juvenile animal study in an appropriate model to characterize the impact of meloxicam on the developing kidney, liver, lung, and testes to support clinical studies in pediatric patients under three years of age.

14. Comments to the Applicant

None.

15. References

None.

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/s/

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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
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Cross-Discipline Team Leader and Division Director Summary Review

Date	June 26, 2020
From	Renee Petit-Scott, MD; Martha Van Clief, MD; Rigoberto Roca, MD
NDA Number	211988
Applicant	Heron Therapeutics, Inc.
Date of Original Submission	October 30, 2018 Complete Response Letter issued April 30, 2019
Date of Complete Response Submission	September 26, 2019
PDUFA Goal Date	June 26, 2020 (includes a 3-month clock extension)
Proprietary Name	Zynrelef™
Established or Proper Name	Bupivacaine and Meloxicam solution.
Dosage Form	Solution for instillation.
Applicant Proposed Indication	(b) (4)
Applicant Proposed Dosing Regimens	Single dose administration for the following doses: – 400 mg bupivacaine and 12 mg meloxicam – 300 mg bupivacaine and 9 mg meloxicam – 60 mg bupivacaine and 1.8 mg meloxicam
Regulatory Action	Complete Response.

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CDTL=Cross-Discipline Team Leader

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

OPDP=Office of Prescription Drug Promotion

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OSE= Office of Surveillance and Epidemiology

OSI=Office of Scientific Investigations

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1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

This is the second review cycle for NDA 211988 and the benefit:risk calculus is still such that the risks associated with administration of HTX-011, proposed tradename Zynrelef™, for postsurgical analgesia continue to outweigh the clinical benefits. The Applicant has not adequately addressed the deficiencies discussed in the Complete Response Letter issued on April 30, 2019, including inadequate data to support exposure to excipients and drug product specifications, and the application is not approvable. A thorough discussion of the identified nonclinical issues is included in Sections 4 and 14 of this review.

The following discussion is adapted from Dr. Martha Van Clief's Cross-Discipline Team Leader Review and Dr. Renee Petit-Scott's clinical review completed during the initial NDA review cycle.

HTX-011, developed by Heron Therapeutics, Inc (Heron), is a fixed-dose combination product composed of bupivacaine and meloxicam in a proprietary Biochronomer® vehicle to allow extended release of the drug product beyond that currently provided by administration of immediate-release bupivacaine. The proposed indication for HTX-011 is (b) (4)

(b) (4) The standard of care for most surgical procedures is the administration of local anesthetic medications via a variety of routes, including wound infiltration, peripheral nerve blocks, neuraxial blocks, and continuous infusion via indwelling peripheral nerve catheters. The limitation of the currently available local anesthetics is their relatively short duration of action and limited postsurgical analgesia.

The results of the HTX-011 drug development program support an analgesic benefit over saline placebo and bupivacaine HCl wound infiltration for up to 72 hours post-operatively in two surgical models, unilateral bunionectomy, HTX-011 60 mg/1.8 mg evaluated in Study HTX-011-301 and open unilateral inguinal hernia repair (or herniorrhaphy) with mesh, HTX-011 300 mg/9 mg evaluated in Study HTX-011-302. Several opioid-related efficacy endpoints reached statistical significance as well, including proportion of patients who were opioid-free through 72 hours and median time to first opioid rescue use. The results of Study HTX-011-209, Cohort 2, a Phase 2b in patients undergoing total knee arthroplasty (TKA), also support the postsurgical analgesic benefit of HTX-011 compared to saline placebo. Because statistical significance was not reached in the comparison of HTX-011 to bupivacaine, in combination with lack of adequate nonclinical data to support the systemic safety of the maximum proposed dose of HTX-011, 400 mg/12 mg, Dr. Petit-Scott did not recommend approval of this dose during the initial review cycle. In the NDA resubmission, however, Heron provided additional nonclinical data to support this highest proposed dose, and the pharmacology-toxicology and clinical pharmacology review teams conclude HTX-011 400 mg/12 mg can be approved for use in patients undergoing total knee arthroplasty based on this data. Dr. Petit-Scott concurs with the teams' assessment, acknowledging that while the regulatory threshold for approval does not require superiority to an active comparator, improved analgesia over saline placebo is likely not clinically significant.

When administered to patients undergoing a bunionectomy, open inguinal hernia repair with mesh, or TKA, the clinical risks of HTX-011 administration include impaired healing of the surgical wound, local anesthetic systemic toxicity (LAST), and the cardiovascular and gastrointestinal adverse events associated with administration of NSAID medications and described in the Mobic® label boxed warnings.

There was an increased incidence of clinically relevant wound-related adverse events in Study HTX-011-301 in patients undergoing bunionectomy, as discussed in detail in Dr. Petit-Scott's review. Approval was still recommended, however, based on the proposed rationale and mitigation strategies, as well as the relatively short-term duration of the adverse events and the fact that there were no reports of osteomyelitis, a more concerning adverse event. There was a total of seven patients with either mal-union or delayed bone healing as identified in post-operative x-rays. Three patients in the HTX-011 treatment group experienced mal-union; two were thought to be due to poor compliance with post-operative care and one was due to trauma (stubbed operative toe on furniture). Four patients had delayed bone healing; one each in the HTX-011 and saline placebo treatment groups and two in the bupivacaine HCl treatment group. At the end of the study, there were three patients in the HTX-011 treatment group with mal-union, and one patient in the bupivacaine treatment group with delayed healing.

There were no clinically significant differences in the incidence of wound-related adverse events reported in Study HTX-011-302 or Study HTX-011-209. There were clinically significant wound-related adverse events reported in the other soft tissue models, including complete abdominoplasty; however, those can be mitigated with limited surgical procedure indications.

In general, there did not appear to be any patients in the Phase 2b study and the two Phase 3 studies who experienced a clinically significant episode of LAST. The reported mean maximum concentration, C_{max} , for bupivacaine after administration of HTX-011 60 mg/1.8 mg in patients undergoing bunionectomy was 33 ng/mL with a mean time of maximum concentration, T_{max} , of 3 hours. The mean C_{max} for bupivacaine after administration of HTX-011 300 mg/9 mg in patients undergoing open inguinal hernia repair with mesh was 271 ng/mL with a mean T_{max} of 18 hours. There was a single patient in Study HTX-011-302 with a C_{max} greater than 1000 ng/mL (measured 1290 ng/mL at 24 hours, estimated 1310 ng/mL at 33 hours), who experienced syncope approximately five hours after study drug administration. The investigator felt the adverse event was unlikely related to study drug administration, which appears a reasonable conclusion since symptoms did not occur at C_{max} . The incidence of LAST-related adverse events appeared to be similar in the bupivacaine HCl treatment group compared to the HTX-011 treatment group. In Study HTX-011-209, which evaluated the highest proposed dose of HTX-011, there were no reported cases of LAST; however, of the studies which evaluated this dose, the TKA study reported the highest individual C_{max} values. Specifically, there were 10 patients with a C_{max} value greater than 1000 ng/mL, and 6 had T_{max} later than 24 hours post-operatively. In general, there did not appear to be an increased incidence in LAST-related adverse events in these 10 patients compared to patients with C_{max} values less than 1000 ng/mL. The risk of delayed LAST associated with bupivacaine products characterized by an extended-release profile is a clinical concern, particularly because many patients will be in an unmonitored setting at this time. This risk, however, can be mitigated by adequate safety monitoring and limiting the use of HTX-011 to the surgical populations most extensively evaluated, bunionectomy, open inguinal hernia repair with mesh, and TKA, and providing detailed discharge instructions such that patients and caregivers are confident they are able to recognize the early signs and symptoms of bupivacaine-induced neurotoxicity.

Regarding the need for the NSAID boxed warnings included in the Mobic® label, the risk for development of cardiovascular (CV) thrombotic and gastrointestinal (GI) bleeding, ulceration, or perforation events after a single administration of HTX-011 is low due to the lower systemic exposure compared to repeated oral meloxicam administration. Review of the observed adverse events across drug development did not identify a single case of a CV thrombotic event or a GI bleed, ulceration, or perforation. These results are reassuring and support the safe use of HTX-011 for the indicated surgical procedures; however, all NSAID-containing products must include the boxed warnings in the label, because it is not clear whether a safe level of exposure exists that would negate these risks.

The clinical benefits of HTX-011 administration during bunionectomy, open inguinal hernia repair with mesh, and TKA outweigh the clinical risks discussed and include a safe and novel route of administration, extended duration of postsurgical analgesia, and an additional analgesic treatment option. A main advantage of HTX-011 over other currently available bupivacaine products is the proposed route of administration, instillation, using a needle-less Luer lock syringe with unique applicator. Because a needle is not used for administration, the risk of inadvertent intravascular administration and catastrophic LAST is minimal, thereby increasing the margin of safety of this bupivacaine-based product. Intravascular and systemic absorption is still a concern in the setting of large doses or administration in areas of increased vascularity; however, these can be mitigated with clear language in the label.

From a clinical perspective, there were no deficiencies identified that preclude approval. Administration of HTX-011 has demonstrated safe and efficacious postsurgical analgesia after bunionectomy, open inguinal hernia repair with mesh, and TKA for up to 72 hours, and a reduction in postsurgical opioid analgesic use compared to those treated with saline placebo. However, based on unresolved nonclinical deficiencies, the application will receive a Complete Response.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute postsurgical pain can be self-limiting and may often only require short term treatment. However, the duration of treatment may vary depending on the specific surgical procedure. • Inadequate management of postsurgical pain is a serious condition and may result in delayed recovery, ineffective rehabilitation, and extended hospitalization. • Inadequate pain management can result in postsurgical complications, such as, pneumonia, deep venous thrombosis, infection, delayed healing, or development of a chronic pain condition, resulting in emotional suffering and	Effective management of acute postsurgical pain is essential to prevent the development of postsurgical complications, chronic pain conditions, and opioid use disorder.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	increased financial costs.	
Current Treatment Options	• Current treatment options for postsurgical pain include the following: - opioid analgesics - non-opioid analgesics - local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia - multimodal therapies - alternative therapies, including acupuncture and massage • Opioid analgesics are first-line therapy for post-surgical pain. However, they are associated with undesirable side effects, such as, sedation, nausea, vomiting, and constipation. The use of opioid analgesics for postsurgical pain may lead to long-term use and abuse. • Non-opioid analgesics alone are usually inadequate for postsurgical pain management. More often they are used as adjuncts to reduce the need for opioid analgesics. • Local anesthetic medications administered via infiltration or nerve block is preferred, when applicable, because they can eliminate the need for opioid analgesics. However, the limitation of immediate-release local anesthetics is their limited duration of action, generally 8 to 12 hours post-operatively depending on the route of administration. • Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. • There are currently no approved local anesthetics with an extended-release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a	The current treatments for postsurgical analgesia have serious drawbacks. Specifically, opioid analgesics have undesirable adverse reactions and their use may lead to opioid use disorder. In general, non-opioid analgesics are inadequate for postsurgical pain management, except for minor procedures. Local anesthetics are effective, but have a limited duration of action that does not meet the need for several days or more of analgesia. Reformulated, extended-release local anesthetics may address an unmet need if the duration of analgesia can cover the period of moderate to severe postsurgical pain. While there are several marketed, approved bupivacaine products for use in the management of postsurgical pain, none have an extended-release profile that reliably prolong postsurgical analgesia beyond that observed after administration of immediate-release bupivacaine.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dilute concentration of bupivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to reliably prolong the duration of action of immediate release bupivacaine.	
Benefit	• The Applicant conducted one Phase 2b and two Phase 3 studies to evaluate the safety and effectiveness of HTX-011 in patients undergoing TKA, bunionectomy, and open inguinal hernia repair with mesh. All three studies were designed as placebo and active-controlled (bupivacaine HCl) studies in adult patients with acute postsurgical pain. • The primary efficacy endpoints, as well as key secondary endpoints, in all three studies demonstrated statistical significance. • In the Phase 3 studies, HTX-011 demonstrated superior postsurgical analgesia through 72 hours compared to bupivacaine HCl, a more clinically meaningful endpoint than comparison to saline placebo, which is a treatment not generally recommended for the management of postsurgical pain. In the Phase 2b study in patients undergoing TKA, administration of HTX-011 did not demonstrate improved analgesia over bupivacaine, an issue discussed in Dr. Petit-Scott's clinical review. • Additional opioid use endpoints also demonstrated statistical, and clinical significance, including mean total opioid consumption through 72 hours in the Phase 3 studies, and through 24 hours in the TKA study, and proportion of opioid-free patients in the Phase 3 studies. • Bupivacaine has been used for decades in the treatment of postsurgical pain and has a well-established safety profile. • Meloxicam is an orally administered NSAID indicated once daily for the treatment of a variety of arthritic conditions. Like other NSAID medications, orally administered meloxicam inhibits cyclooxygenase enzymes (COX-1 and	Approval of HTX-011 would offer clinicians an additional bupivacaine product to administer for postsurgical pain management after bunionectomy, open inguinal hernia repair with mesh, and TKA. The Phase 2b and Phase 3 clinical studies conducted by the Applicant included a bupivacaine control treatment group, such that the efficacy and safety comparisons allowed a more relevant assessment of the true clinical benefit of HTX-011 over standard of care bupivacaine wound infiltration. There was a statistically significant decrease in post-operative opioid analgesic use through 72 hours in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine after bunionectomy and open inguinal hernia repair with mesh. The largest difference in opioid use between treatment groups, however, was early in the post-operative period, i.e., < 24 hours, which likely contributed to the persistent statistical significance through 72 hours. There was a trend toward a lower incidence of opioid-related adverse events in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine; however, review of concomitant medications indicated less impressive differences in the treatment of opioid-related adverse events, such as post-operative nausea and vomiting. Additionally, there were confounding variables that impacted the clinical significance of the reported opioid-related adverse events, including administration of concomitant sedation or general anesthesia, lack of stratification of patients with a history of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	COX-2), resulting in decreased production of inflammatory prostaglandins and ultimately analgesia. The mechanism of action of action when administered locally in HTX-011 is not completely understood, but may involve anti-inflammatory actions and/or maintenance of physiologic pH in the setting of tissue injury, resulting in more nonionized bupivacaine available to penetrate nerves and inhibit conduction of sensory information. • The Applicant has demonstrated, in two factorial studies, improved clinical benefit of HTX-011 compared to treatment with bupivacaine (the disease-active ingredient) and meloxicam individually in the Biochronomer® vehicle after bunionectomy and open inguinal herniorrhaphy.	post-operative nausea and vomiting, and patient factors, such as gender and smoking history. The totality of the impact of adequate postsurgical pain management on health care outcomes is immeasurable and the benefits are likely to extend beyond individual patient outcomes, potentially impacting overall cost and societal burden of poorly managed pain.
Risk and Risk Management	The three safety issues of greatest concern with administration of HTX-011 include impaired healing of the surgical wound, the development of LAST, CV thrombosis and GI-related adverse events as described in the Mobic® label boxed warnings. <u>Wound Healing</u> • An extensive review of surgical wound healing data indicated that there is an increase in wound-related adverse events in patients treated with HTX-011 after certain surgical procedures, specifically bunionectomy and abdominoplasty. • The increased incidence of wound-related adverse events in patients undergoing bunionectomy may be related to an excipient in the Biochronomer formulation or more likely due to leakage of excess HTX-011 from the surgical wound. However, as noted in Dr. Petit-Scott's clinical review, the majority of adverse events were mild in severity, resolved by the end of the study, and did not result in clinically significant adverse boney findings. • The wound-related adverse events observed in patients undergoing complete abdominoplasty may have been due	The majority of reported wound-related adverse events in patients undergoing bunionectomy were graded as mild in severity and resolved by the end of the study. The incidence of adverse events related to bone healing or hardware failure was similar across treatment groups. A possible explanation for the increased incidence of wound-related adverse events in patients undergoing bunionectomy is that excess HTX-011 leakage from the small surgical wound may have resulted in poor approximation of the wound edges, local inflammation, and delayed soft tissue healing. A possible explanation for the increased incidence of wound dehiscence in patients undergoing complete abdominoplasty may be due to the injection route of administration, thereby disrupting the posterior rectus sheath plication. The following mitigation strategies to minimize the wound-related adverse events will be included in the product label (final language to be determined): • Avoid excess HTX-011 administration; i.e., instill only as much

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to disruption of the posterior rectus plication, route of administration (injection and instillation), or umbilicus repositioning. HTX-011 is not recommended for use in this surgical model based on insufficient safety and efficacy data. <u>LAST</u> - Factors influencing the development of LAST include the site of administration and total dose administered. The proposed maximum dose of bupivacaine in HTX-011 400 mg/12 mg is higher than the recommended dose in the Marcaine™ product label, 175 mg without epinephrine. Use of a higher than currently recommended dose may lead to an increased incidence of LAST depending on the vascularity of the surgical site. - Because the PK profile of HTX-011 is variable, use of the product in other surgical models or for other painful conditions is not recommended without additional clinical data. While bupivacaine has a long history of clinical use and the safety profile is well-established, it is highly cardiotoxic due to its strong affinity for cardiac Na⁺ channels and the high degree of protein binding. Systemic exposure to increased amounts of bupivacaine poses the greatest risk for the development of toxicity and HTX-011 instillation into highly vascular sites is likely to increase the risk above what has been characterized in the Applicant's clinical studies. - An additional concern regarding the variable PK profile of HTX-011 is the likelihood of patients being in an unmonitored setting around C_{max}, a time when the risk of toxicity is the highest. This can in part be mitigated by adequate and comprehensive patient education regarding the signs and symptoms associated with bupivacaine toxicity. <u>CV Thrombosis and GI-related Adverse Events</u>	volume as the surgical space will accommodate and to coat the tissues - Ensure complete closure of the surgical wound and approximation of the wound edges - Only administer HTX-011 during surgical procedures for which the safety and efficacy has been thoroughly evaluated. Despite the higher dose of bupivacaine administered in HTX-011 400 mg/12 mg than is currently approved in the Marcaine™ label, the risk of developing LAST appears low. In general, the maximum systemic exposure after administration of HTX-011 400 mg/12 mg was below the threshold, 1000 to 2000 ng/mL, for local anesthetic-induced neurotoxicity in the majority of treated patients. In the Phase 2b and Phase 3 clinical studies, there did not appear to be any cases of clinically significant LAST and the incidence of potential LAST-related treatment-emergent adverse events was similar between the HTX-011 and bupivacaine HCl treatment groups. The development of LAST with use of this drug product can be mitigated by the following: - Narrow postsurgical indication, based on safety data captured from adequate and well-controlled studies - Avoid administration in highly vascular surgical sites (e.g., intrathoracic) or procedures (e.g., multilevel spinal fusion with instrumentation) - Avoid administration on denuded tissues, such as burns - Maximum recommended dose 400 mg/12 mg The proposed route of administration of HTX-011 offers a margin of safety over that of other injectable bupivacaine-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• NSAID use and the resulting inhibition of the cyclooxygenase enzymes has been linked to CV thrombotic events, including myocardial infarction (MI) and graft stenosis after coronary artery bypass graft surgery, and GI-related adverse events, including bleeding, ulceration, and perforation of the stomach or intestines. Because meloxicam is an NSAID, oral administration can result in a CV thrombotic event and GI-related adverse events and the product label includes the boxed warnings required for NSAID medications. • While there were no reported adverse events related to CV-thrombosis or the GI tract in patients treated with HTX-011 across clinical development, the boxed warnings are likely required for the HTX-011 product label because it is unclear whether a safe level of exposure exists such that the risks are negligible.	containing products. Specifically, because HTX-011 is administered via a needle-less Luer lock syringe, the risk of inadvertent intravascular injection, and hence catastrophic LAST, is low. While there were no reported adverse events concerning for CV thrombosis or GI-related adverse events after administration of HTX-011 and the overall systemic meloxicam exposure is lower than that observed after oral administration, it is not clear if there is a level of exposure that would negate the risk and eliminate the need for the boxed warnings in the label. Therefore, the NSAID boxed warnings are required in the HTX-011 label.

2. Background

This document will serve as the Cross-Discipline Team Leader (CDTL) and Division Director Summary review of new drug application (NDA) 211988 for the decision on regulatory action following resubmission on September 26, 2019.

NDA 211988 was initially submitted for approval through the 505(b)(2) regulatory pathway on October 30, 2018, for Zynrelef™, also referred to as HTX-011, a bupivacaine and meloxicam solution, indicated for the management of postsurgical pain. The Applicant, Heron Pharmaceuticals, Inc. (Heron), was relying on the Agency's previous findings of safety and efficacy for Marcaine™ (NDA 01964) and Mobic® (NDA 020938). Based on unresolved issues regarding drug product quality and nonclinical safety concerns, the application received a Complete Response Letter (CRL) on April 30, 2019. The following is a summary of the identified deficiencies, by discipline, and the information needed to adequately address them (refer to the CRL for the detailed listing of identified deficiencies).

Product Quality

1. Leachables study data was inadequate to support the proposed shelf-life of the drug product, and the lack of adequate study data prevented a definitive toxicological risk assessment.
 - Information needed to address this deficiency: Provide test data for all potential leachables, identified through the various extraction studies, monitored at release and at multiple timepoints during the stability testing of HTX-011 batches using validated analytical methods.
2. Inspection of the manufacturing site, (b) (4) identified concerns that were conveyed to the representative of the facility.
 - Information needed to address this deficiency: Satisfactory resolution of these deficiencies is required before this application may be approved.

Nonclinical

3. There were inadequate data to support the safety of the dimethyl sulfoxide (DMSO) or triacetin. The levels in the drug solution exceeded the maximum potency listed in the CDER Inactive Ingredient Database (IID) and were, therefore, considered novel. The NDA was lacking discussion of the impact of these two excipients on the standard reproductive and developmental battery of studies.
 - Information needed to address this deficiency: Submit adequate data to fully characterize the impact of the proposed doses of DMSO and triacetin on all endpoints normally characterized via the standard battery of reproductive and developmental toxicology studies. Should this be addressed via literature, the adequacy of the literature based on current standard study protocols must be justified and copies of all referenced literature must be submitted. In the absence of adequate published data, GLP nonclinical toxicology studies should be completed.
4. The toxicological risk assessment for the excipient maleic acid, which exceeds the maximum potency listing in the CDER Inactive Ingredients Database (IID), did not

address the potential impact of maleic acid on embryo-fetal development in a second species (typically rabbit).

- Information needed to address this deficiency: Adequate justification for the safety of the proposed maximum daily dose of maleic acid.
5. There were inadequate data to qualify the proposed drug product degradant (b) (4) which exceeds the ICH Q3B(R2) qualification threshold.
 - Information needed to address this deficiency: Either tighten the drug product specification (b) (4) to NMT (b) (4) % or provide adequate qualification in accordance with ICH Q3B(R2).
 6. There were inadequate data to support the safety of the drug product specification for (b) (4).
 - Information needed to address this deficiency: Either tighten the specification (b) (4) to be within the qualification threshold of NMT (b) (4) % or provide adequate qualification in accordance with ICH Q3B(R2).
 7. There were inadequate leachable data to permit substantive toxicological evaluation of the safety of the container closure system (b) (4) for this drug product.
 - Information needed to address this deficiency: Conduct new leachables studies based on all of the extractables identified in Extractable Study 3 identified above the safety concern threshold (SCT) (b) (4) according to USP <1663> and <1664>. In addition, since Extractable Study 3 did not address non-volatile compounds, conduct new leachable studies based on the non-volatile compounds identified in Extractable Studies 1 (RPT-701) and 2 (RPT-693).

An additional deficiency was identified by the review team in the Center for Devices and Radiological Health and involved inadequate information to ensure syringe tip cap sterility.

While not identified as a deficiency contributing the CR action, the pharmacology-toxicology review team did note that the nonclinical data did not provide adequate coverage for the systemic safety of bupivacaine administered via HTX-011 at the proposed maximum dose of 400 mg and the following comment was included in the CRL.

Although the current nonclinical data appear to support the safety of bupivacaine when the product is dosed up to 300 mg, the data do not provide adequate coverage for the maximum AUC_{0-24h} via this drug product at your proposed maximum dose of 400 mg bupivacaine. Because your drug product exposures above 300 mg of bupivacaine via this drug product will exceed that of the referenced drug product, additional data will be required to support any proposed dose above 300 mg bupivacaine.

During the original NDA review cycle, Dr. Renee Petit-Scott, clinical reviewer, recommended approval of HTX-011 60 mg/1.8 mg and 300 mg/9 mg for the management of postsurgical pain following unilateral bunionectomy and unilateral open inguinal hernia repair with mesh, respectively. She concluded that when formulated in the proprietary Biochronomer vehicle, bupivacaine and meloxicam did appear to demonstrate extended release profiles, which resulted in statistically and clinically significant postsurgical analgesia through 72 hours. In

addition to a reduction in post-operative mean pain intensity scores, Dr. Petit-Scott noted that administration of HTX-011 in the two evaluated surgical models resulted in decreased mean post-operative opioid use and a trend toward a lower incidence of opioid-related adverse events.

Dr. Petit-Scott did not recommend approval of HTX-011 400 mg/12 mg for administration during any procedure evaluated during clinical development for three reasons. First, she concluded that the evaluation of safety and efficacy of this dose was in a low number of patients in adequate and well-controlled studies. At that time, there were only 58 patients who underwent total knee arthroplasty (TKA) in Study HTX-011-209, Cohort 2, and 17 patients who underwent complete abdominoplasty in Study HTX-011-C2015-203 who received HTX-011 400 mg/12 mg via the proposed route of administration. Dr. Petit-Scott did not consider the evaluation of HTX-011 400 mg/12 mg in patients undergoing bilateral augmentation mammoplasty in Study HTX-011-211 supportive of a single administration given the dose was divided between the breast pockets and separated in time. Second, the variable PK data after administration of HTX-011 400 mg/12 mg made extrapolation to other surgical procedures challenging and unsafe. And lastly, based on the nonclinical and clinical pharmacology data submitted, Dr. Petit-Scott did not feel that the systemic safety profile for HTX-011 400 mg/12 mg had been adequately established.

Heron proposes

(b) (4)

The regulatory history and Applicant interactions following issuance of the CRL are summarized in the following table.

Table 1. Key Regulatory History Subsequent to Issuance of CR Letter

Meeting/Communication/Date	Event/Key Issues Identified
Complete Response Letter, April 30, 2019	Product quality and nonclinical deficiencies identified.
Teleconference, May 29, 2019	Clarification regarding identified product quality and leachables deficiencies, and findings from the (b) (4) manufacturing site inspection.
Type A Post-Action Teleconference, August 7, 2019	The discussion during the meeting focused on the following: – adequacy of actions taken (b) (4) following the inspection – acceptability of the proposed theoretical maximum intended dose volume – acceptability of dynamic viscosity and syringeability studies

Meeting/Communication/Date	Event/Key Issues Identified
	– acceptability of new stability data – adequacy of DMSO and triacetin evaluation – specification for (b) (4) – adequate support for the 400 mg/12 mg dose – adequacy of leachables and toxicological evaluations – calculation of AET – syringe tip cap sterility assurance – safety update required with NDA resubmission
Amended iPSP, October 11, 2019	Amended iPSP with revised milestones due to delayed juvenile animal studies.
NDA 211988 Resubmission, September 26, 2019	The Division determined the submission was a complete response and acceptable for review. A PDUFA goal date of March 26, 2020, was set.
Three-month clock extension, February 10, 2020	On December 23 and 31, 2019, the Division received submissions which constituted major amendments, resulting in a three-month clock extension. A PDUFA goal date of June 26, 2020, was set.

For information regarding the regulatory history and communications that were reviewed during the first cycle, refer to the clinical review completed by Dr. Petit-Scott on April 30, 2019.

3. Product Quality

Based on evaluation of the information included in the NDA resubmission, the Applicant adequately addressed the outstanding product quality issues that contributed to the CR action during the initial review cycle. The following is a summary of the product quality review, adapted from the quality review team.

Product Overview

Zynrelef is a fixed-dose combination product intended for soft tissue instillation and periarticular instillation use. The drug product containing sterile non-aqueous viscous solution of bupivacaine and meloxicam in a vial is supplied as kit for hospital use, along with device components required for preparation and administration in carton. The device components included in the kit for preparation and application of the drug solution include syringe(s), tip cap(s), vented vial spike [VVS], Luer lock applicator(s) [LLA(s)]. Zynrelef is supplied in four different dose strengths, i.e. 60 mg/1.8 mg, 200 mg/6 mg, 300 mg/9 mg, or 400 mg/12 mg of bupivacaine base and meloxicam respectively. The syringes are made of (b) (4) barrel and (b) (4) piston; the tip cap and LLAs are made of (b) (4) and VVS are made of (b) (4) materials.

Facilities Review/Inspection

Upon follow-up inspection of the drug manufacturing facility ((b) (4) FEI: (b) (4)), deficiencies identified during earlier inspection were adequately addressed and the facility portion is now acceptable for manufacturing of the drug product at (b) (4) kg batch size. (b) (4)

Quality Assessment Overview

The drug product is a sterile, viscous, non-aqueous solution of bupivacaine and meloxicam. Each mL of the solution contains active ingredients bupivacaine 29.25 mg and meloxicam 0.88 mg; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg), triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg).

– Drug substances

The drug substances are referenced to DMF (b) (4) (Bupivacaine) and DMF (b) (4) (Meloxicam) that were reviewed as adequate to use in the manufacture of the drug product. Bupivacaine has a retest period of (b) (4) months ((b) (4) years) and meloxicam has a retest period of (b) (4) months ((b) (4) years). Tri(ethylene glycol) poly(orthoester), designated as AP135, is considered a novel excipient. The Applicant provided adequate information on synthesis and characterization of impurities in AP135, along with toxicological assessment in support of its safety.

– Drug product

The drug product is prepared (b) (4)

The four dosage strengths are prepared by filling appropriate volumes of the solution in either a 10 mL or 20 mL (b) (4) clear glass vials, capped with 20 mm (b) (4) gray (b) (4) stopper (b) (4) and secured with a 20 mm aluminum overseal.

In-use compatibility study reports, for the device components and drug product during preparation and use, included in the submission indicated that the device components are compatible with the drug solution.

Analytical methods used for monitoring the quality of the drug substances and finished drug product; including test methods used for monitoring elemental impurities and leachables in the drug product and tests for sterility and endotoxin content are adequately validated. Suitability of primary container closure system (CCS), clear USP (b) (4) glass vials sourced from (b) (4) 20 mm (b) (4) stoppers (b) (4) is adequately justified through stability testing of the finished drug product. The new information provided in the resubmission, on leachables and the root cause analysis for

sources [REDACTED] (b) (4) is adequate to address the product quality deficiency identified during the initial review cycle.

Additional information provided on the tip cap (a 510(k) cleared device component) ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life and the device is safe for use and addresses the CDRH deficiency identified in CRL.

I concur with the conclusion of the product quality review team that there are no outstanding issues that would prevent approval.

4. Nonclinical Pharmacology/Toxicology

The following information is adapted from the review completed by Dr. Jaime D'Agostino.

The drug product formulation contains several new excipients, defined by the FDA guidance document as excipients used at higher doses, concentrations, or routes of administration than previously approved drug products. Specifically, the proposed doses of AP135, DMSO, triacetin, and maleic acid exceeded levels present in FDA-approved drug products as per the CDER Inactive Ingredients Database (IID). The Applicant was informed of the need to adequately qualify the safety of these new excipients early in their development program. In the initial NDA submission, adequate data were provided to characterize the reproductive and developmental safety profile of AP135 at the maximum recommended human dose (MRHD). However, the Applicant did not adequately justify the safety of DMSO, maleic acid, and triacetin with respect to the standard reproductive and developmental toxicology battery endpoints, which contributed to the decision to issue a CR action. The Applicant submitted additional reproductive and developmental toxicity data in the NDA resubmission, which addressed some of the concerns; however, adequate bridging data were not provided nor data to support a waiver of embryofetal studies in a second species for one excipient.

The drug substance impurity and drug product degradant specifications are acceptable with the exception of the drug product specification [REDACTED] (b) (4). The deficiency related to the drug product degradant [REDACTED] (b) (4) has been addressed by reducing the specification to NMT (b) (4)%, which is acceptable based on the qualification thresholds in ICH Q3B(R2). The Applicant did not adequately address the specification [REDACTED] (b) (4) in the drug product. Although the Applicant hypothesizes [REDACTED] (b) (4) data to support this hypothesis was not provided.

In total, eight individual leachables were identified above the analytical evaluation threshold (AET) across the five leachable studies and the combined level [REDACTED] (b) (4) was above the AET in one leachable study. The Applicant provided a detailed risk assessment for the leachables and permissible daily exposures (PDEs) were derived for the compounds based on the available data. The maximum detected levels of the leachables were all below the calculated PDEs and are not expected to be of a safety concern.

From the nonclinical pharmacology toxicology perspective, adequate data have not been submitted to permit a recommendation of approval at this time and a complete response is recommended. The following outstanding deficiencies have been identified (summarized):

1. The Applicant has not provided adequate data to support the request for a waiver of reproductive and developmental studies for triacetin.
2. The Applicant has not provided an adequate scientific bridge to the referenced oral reproductive and developmental studies submitted to qualify the safety of DMSO exposure via the drug product.
3. The Applicant has not provided adequate data to support the proposed drug product specification (b) (4) at NMT (b) (4)%. The nonclinical and clinical lots tested to date in your development program did not contain this high of a percentage (b) (4) and therefore does not qualify this specification.
4. The embryofetal development study in rabbits tested maleic acid via an oral route of administration rather than the proposed route of administration of HTX-011 and the scientific bridge was inadequate to support the conclusion that the study provides adequate characterization of the developmental effects of maleic acid exposures via instillation into a wound.

Although not listed as a deficiency in CRL, the proposed specification for DMSO of (b) (4)% has an upper limit that was not tested in the clinical or nonclinical development programs, and because DMSO may contribute to local tissue toxicity, the specification needs to be revised, a new study is needed to characterize the local effects of the to-be-marketed drug product containing DMSO at the upper limit of the proposed specification, or justification is needed as to why DMSO at (b) (4)% will not contribute to the local tissue effects of the drug product.

In clinical bioavailability studies, the exposure (AUC) to bupivacaine via the drug product formulation at the proposed maximum daily dose of 400 mg bupivacaine exceeded that of the referenced drug products (e.g., Marcaine), and therefore additional data were needed to qualify the systemic safety of bupivacaine for the proposed clinical use. The pivotal 28-day nonclinical studies in rats and dogs included exposure data at 24 and 48 hours but not AUC_{inf}. Because the exposure in rats was lower than in humans (~ 0.5x and 0.3x for AUC₀₋₂₄ and AUC₀₋₄₈, respectively), the Applicant conducted a 14-day study in rats by subcutaneous injection (dosing every 48 hours) of HTX formulations containing only bupivacaine (not the to-be-marketed formulation) and used a higher dose than in the previous rat study. The toxicological findings in the 14-day rat study were similar to the results of the 28-day studies, which included an inflammatory response that is consistent with a foreign body reaction and changes in hematology parameters. It is difficult to assess if the magnitudes of the changes are more severe in this study compared to previous studies which used lower doses of bupivacaine due to differences in dosing volumes, formulations, and durations of treatment. The combined male and female systemic exposure (AUC_{inf}) of bupivacaine achieved in the study (52,900 ng*h/mL) was higher than the highest reported bupivacaine exposure reported in the Applicant's clinical studies (Study 209, total knee arthroplasty, 31,173 h*ng/mL) by a factor of ~1.7x.

While the data from the 28-day dog study is not ideal because AUC_{inf} was not calculated, the study provide data in a second species that had similar exposure to bupivacaine over 24 hours as humans exposed to 400 mg bupivacaine (~1x). The only systemic finding in dogs at this exposure level was an increase in reticulocytes. Taken together with the results from the 14-day rat study which achieved a higher exposure multiple, the safety of the 400 mg dose of bupivacaine is supported by the nonclinical data as long as the clinical team does not believe that changes in hematology parameters are of a clinical concern considering the human experience.

In summary, I concur with the pharmacology-toxicology review team that there are unresolved nonclinical deficiencies that preclude the approval of this NDA. It appears, however, that adequate nonclinical data have been provided to support the clinical use of HTX-011 400 mg/12 mg, at such time as the identified deficiencies have been adequately addressed.

5. Clinical Pharmacology

During the initial review cycle, Dr. Suresh Narahariseti concluded that there were no clinical pharmacology issues identified that would have affected the approval of HTX-011. However, he noted in his review that the pharmacology-toxicology team concluded that there were inadequate nonclinical data submitted to support the highest proposed bupivacaine dose of 400 mg in HTX-011. In addition to nonclinical data included in the resubmission to address this concern, Heron provided additional PK information from the published literature to support the bridge for bupivacaine systemic exposure between HTX-011 and bupivacaine HCl. Heron also submitted bioanalytical information from published literature, as well as PK information from Study BUPI-501, a study which evaluated the PK, safety, and efficacy of bupivacaine HCl 0.25% 120 mL (300 mg total dose) infused into inguinal herniorrhaphy wounds over 60 hours.

The following information is adapted from Dr. Narahariseti's review of the clinical pharmacology data provided in the NDA resubmission, with emphasis on the justification for the clinical use of HTX-011 400 mg/12 mg.

- The mean bupivacaine C_{max} value at the highest proposed dose of HTX-011, 400 mg/12 mg in augmentation mammoplasty, is lower than that for bupivacaine HCl in the same surgical procedure, providing supportive PK information for HTX-011 400 mg/12 mg dosing.
- From regulatory perspective, for bioavailability comparison between test and reference products, the accepted PK measures are C_{max} , AUC_{0-t} and AUC_{inf} . However, as mentioned in section 2 Regulatory Background, in the CR letter dated 4/30/2019, the non-clinical team also asked the sponsor to provide adequate coverage for the maximum AUC_{0-24h} .
 - To compare systemic exposure on Day 1 to the overall systemic exposure between HTX-011 and bupivacaine HCl, the ratios of AUC_{0-24h} to AUC_{inf} were compared between two products from NDA clinical trials.
 - For HTX-011, AUC_{0-24h} to overall AUC (AUC_{inf}) ranged between 29 to 51%, while for bupivacaine HCl the values are higher and ranged between 65 to 81%.

- Based on observed lower bupivacaine AUC_{0-24h} / AUC_{inf} ratio-values of HTX-011 compared to bupivacaine HCl, it is a reasonable estimation that the bupivacaine AUC_{0-24h} of HTX-011 at 400 mg/12 mg dose will be lower than that of bupivacaine HCl when given 400 mg/day.
- In the original NDA submission, the Applicant attempted to assess PK dose-linearity of bupivacaine in HTX-011 using PK data from different surgical procedures using different routes of administration, including injection, nerve block, and a combination of instillation and injection. The Applicant concluded that the mean C_{max} and AUC for bupivacaine and meloxicam increased linearly with increasing doses of HTX-011 from 60 mg/1.8 mg to 400 mg/12 mg regardless of the anatomic space, vascularity of the surgical site, or administration technique. However, we determined that bupivacaine and meloxicam PK parameters are significantly different between surgical procedures. The Marcaine label also states that, “the rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution”.
 - In the PK dose linearity assessment of HTX-011, since the surgical procedure-differences is a confounding factor, the dose-linearity assessment of HTX-011 between different procedures is not appropriate. Hence, the PK linearity within-procedure between different HTX-011 doses was assessed. For this assessment, the data was available in herniorrhaphy procedure for two HTX-011 doses, 200 mg/6mg and 400 mg/12 mg; and in bunionectomy for two HTX-011 doses, 60 mg/1.8 mg and 120 mg/3.6 mg. The data from both procedures showed within-procedure dose linearity for both C_{max} and AUC for both bupivacaine and meloxicam of HTX-011 (Clinical pharmacology review, DAARTS 04/10/2019). Based on the data submitted in this review cycle, for bupivacaine HCl also, within procedure dose-linearity was also observed for both C_{max} and AUC in augmentation mammoplasty between 50 and 150 mg.
 - Overall, based on the data available so far from the NDA clinical trials, the ‘within procedure’ PK dose-linearity for bupivacaine was observed up to 400 mg dose for HTX-011 in two procedures, while for bupivacaine HCl up to 150 mg in one procedure.
- In comparison to the calculated 400 mg bupivacaine HCl AUC_{inf} values, the observed HTX-011 AUC_{inf} value is lower by ~18% for abdominoplasty (Study 203); while it is higher by ~40% and ~72%, respectively for augmentation mammoplasty (Study 211) and TKA (Study 209).
- Regardless of whether the Sponsor provided adequate PK information to address the systemic exposure of HTX-011 400 mg dose, the additional nonclinical data included in the resubmission appears adequate to support the systemic safety of this dose.

Refer to the clinical pharmacology review completed by Dr. Narahariseti for additional information regarding the PK profile of all proposed doses of HTX-011.

I concur with Dr. Narahariseti’s conclusion that there are no clinical pharmacology concerns that would prevent approval of HTX-011 at such time as the identified nonclinical deficiencies are adequately addressed.

6. Clinical Microbiology

HTX-011 is not a therapeutic antimicrobial, therefore clinical microbiology data were neither required nor submitted.

7. Clinical/Statistical- Efficacy

The Applicant did not submit additional data from completed clinical studies in the NDA resubmission. Clinical efficacy data reviewed during the initial NDA review cycle included results from two adequate and well-controlled Phase 3 studies, results from an adequate and well-controlled Phase 2b study, and results from two Phase 2 factorial studies conducted to demonstrate the contribution of each component in HTX-011. Refer to the clinical review completed by Dr. Petit-Scott for additional information regarding the efficacy data submitted in support of this application.

In Study HTX-011-301, a Phase 3 study in patients undergoing bunionectomy, a single HTX-011 60 mg/1.8 mg dose was instilled into the proximal and distal ends of the wound, forming rings around the metatarsal. In Study HTX-011-302, a Phase 3 study in patients undergoing inguinal herniorrhaphy, a single HTX-011 300 mg/9 mg dose was instilled at the level below and the level above the fascial plane. Study drug was not administered in the shallow subdermal layer. In Study HTX-011-209, a Phase 2b study in patients undergoing TKA, in Cohort 2, a single HXT-011 400 mg/12 mg dose was instilled directly to the posterior capsule, the anteromedial tissues and periosteum, and the anterolateral tissues and periosteum after cementation of the components. The factorial studies evaluated the individual components of HTX-011 in patients undergoing bunionectomy and inguinal hernia repair.

As described in the clinical and statistical reviews completed during the initial review cycle, approval of HTX-011 60 mg/1.8 mg and 300 mg/9 mg were recommended for use during bunionectomy and unilateral inguinal hernia repair, respectively. Dr. Petit-Scott did not recommend approval of HTX-011 400 mg/12 mg for administration during any evaluated surgical procedure based primarily on the low number of treated patients and the lack of nonclinical supportive data, discussed elsewhere in this review. In lieu of the additional nonclinical information included in the NDA resubmission, however, the benefit:risk calculus has changed and Dr. Petit-Scott, along with Dr. Susan Yost, who reviewed information in the resubmission regarding the acceptability of the HTX-011 400 mg/12 mg dose, conclude that the postsurgical analgesic benefits of HTX-011 400 mg/12 mg outweigh the risks and they recommend approval for use during a single surgical procedure, TKA.

During her review of the data from Study HTX-011-209, Dr. Yost concluded that substantial evidence of efficacy had been demonstrated based on the statistically and clinically significant differences between the HTX-011 400 mg/12 mg and saline placebo treatment groups on the primary and key secondary efficacy endpoints. Specifically, HTX-011 400 mg/12 mg demonstrated improved postsurgical analgesia at rest through 48 hours (the primary efficacy endpoint) and through 72 hours (secondary efficacy endpoint) and with activity through 24, 48, and 72 hours (exploratory efficacy endpoints) compared to saline placebo. Additionally, there were trends toward decreased overall opioid consumption in patients treated with HTX-

011 400 mg/12 mg compared to saline placebo, reaching statistical significance from 0 to 24 hours post-operatively, and a lower incidence of opioid-related adverse events. Administration of HTX-011 400 mg/12 mg did not demonstrate improved (increased) median time to first opioid use compared to saline placebo and no patient in the HTX-011 treatment group was opioid-free through 72 hours. These results suggest that while HTX-011 40 mg/12 mg is an effective postsurgical analgesic, it likely cannot be used as monotherapy in patients undergoing TKA.

Administration of HTX-011 400 mg/12 mg did not demonstrate improved analgesia or decreased opioid consumption at any evaluated time points compared to administration of bupivacaine HCl. Dr. Petit-Scott discussed these findings in her clinical review and expressed concern regarding the true clinical benefit of HTX-011 over standard of care bupivacaine HCl wound infiltration in patients undergoing TKA; however, she also noted that demonstration of efficacy over a placebo treatment in an adequate and well-controlled study meets the regulatory threshold for approval.

It is noted that during the initial review cycle, the statistical review team concluded the following regarding the reported results for Study HTX-011-209, Cohort 2:

Study HTX-011-209 failed to demonstrate a superiority of HTX-011 400 mg/12 mg over bupivacaine on both primary and key secondary endpoints during the 72-hour post-operative period in subjects undergoing TKA. Therefore, this study will not be included in the Clinical Studies, Section 14 of the label per the combination rule.

The Proposed Rule, issued by the Agency on December 23, 2015, to revise the requirements for fixed-combination drugs, states the following, "...a clinical trial comparing the combination to the disease-active ingredient alone would usually be necessary to demonstrate the contribution of each active ingredient. The trial would have to establish enhanced safety or effectiveness of the combination versus the disease-active ingredient alone." Because the Applicant conducted two Phase 2 factorial studies, which demonstrated bupivacaine is the disease-active ingredient and HTX-011 resulted in improved postsurgical analgesia compared to bupivacaine in the Biochronomer vehicle alone, the requirements of the Proposed Rule have been met.

In conclusion, the clinical review team recommends approval of HTX-011 60 mg/1.8 mg, 300 mg/9 mg, and 400 mg/12 mg for administration during bunionectomy, open inguinal hernia repair with mesh, and total knee arthroplasty, respectively, at such time as the identified nonclinical deficiencies have been adequately addressed.

8. Safety

During the initial review cycle, Dr. Petit-Scott concluded that administration of HTX-011 60 mg/1.8 mg and 300 mg/9 mg were safe postsurgical analgesic treatments for patients undergoing bunionectomy and open inguinal hernia repair with mesh, respectively. She noted that the safety issues of greatest concern associated with administration HTX-011 include the

potential adverse impact on surgical wound healing and the risk for development of local anesthetic systemic toxicity (LAST).

There did appear to be an increased incidence of wound-related adverse events primarily observed in patients undergoing bunionectomy. However, Dr. Petit-Scott concluded that HTX-011 should be approved for this indication for four reasons. First, the Applicant's explanation for leakage of excess HTX-011 from the wound potentially contributing to the development of local inflammatory changes in the short-term (less than 42 days) is reasonable and can be mitigated by language in the drug product label. Second, the majority of wound-related adverse events were mild and resolved by the end of the study. Third, there were no reported cases of osteomyelitis. Of the identified boney changes, the incidences between groups was similar and not clinically significant. And lastly, the surgical wounds may have been "over-graded" and reported as adverse healing, which may not have occurred in a standard clinical setting.

In patients undergoing TKA in Study HTX-011-209, there was an increased incidence in some wound-related adverse events; however, more clinically significant adverse events such as cellulitis were not consistently reported with an increased incidence in the HTX-011-treated patients. Furthermore, it appears that the surgical wound assessments, using the Southampton Wound Scoring System conducted at 72 hours and on Days 10 and 28 for all patients and at 96 and 120 hours for patients still hospitalized, indicated that more patients treated with HTX-011 400 mg/12 mg had a Grade 0 (normal healing) finding as the worst post-baseline assessment compared to patients treated with saline placebo or bupivacaine HCl. The percentage of patients with normal healing documented on Day 28 was similar across all treatment groups. Bone healing assessments were not conducted during this study, but there were no reported fractures, cases of osteomyelitis, or failure of the prosthetic joint.

Regarding the safety profile of HTX-011 in soft tissue surgical models, there did not appear to be an increased incidence of clinically significant wound-related adverse events in patients undergoing inguinal hernia repair, the only indicated soft tissue procedure recommended for approval. In Study HTX-011-C2015-203, patients undergoing complete abdominoplasty, there was an increased incidence of wound dehiscence in patients treated with HTX-011 300 mg/9 mg administered via a combination of injection and instillation, which may have been due to disruption of the posterior rectus plication and umbilicus repositioning. The risk of this adverse event can be mitigated by limited indicated surgical procedures.

The second main safety concern associated with HTX-011 administration is the risk of LAST. Because HTX-011 300 mg/9 mg and 400 mg/12 mg contain higher recommended doses of bupivacaine than currently approved for Marcaine, the following discussion will focus on the risk of developing LAST after administration of those doses. As noted in Dr. Petit-Scott's and Dr. Narahariseti's reviews, there was wide variability in measured PK parameters for each study in which the highest dose of HTX-011, 400 mg/12 mg, was administered via instillation, suggesting that extrapolation of PK data for different surgical sites is not feasible and each proposed indication will likely require clinical studies.

The challenge with extended or delayed release bupivacaine products is that the local efficacy is unrelated to the systemic concentration, such that the recommend time for safety monitoring can be difficult to predict. The systemic bupivacaine concentration at which LAST can develop is debatable and appears to depend on many factors, including the dose, route, and site of administration and the underlying medical condition of the treated patient. Historically, ≥ 2000 ng/mL was the systemic level concerning for the development of neurotoxicity and ≥ 4000 ng/mL for the development of cardiotoxicity. As described in the article by Scott *et al* (1989), however, bupivacaine toxicity can develop at systemic concentrations >1000 ng/mL.

Dr. Petit-Scott noted in her clinical review that there did not appear to be an increased incidence in potential LAST-related adverse events in patients treated with HTX-011 300 mg/9 mg compared to patients treated with saline placebo or bupivacaine HCl in Study HTX-011-302. There was an increased incidence of hypotension, paresthesia oral, sinus arrhythmia, and sinus bradycardia in the HTX-011 treatment group compared to the bupivacaine HCl treatment group; however, the differences were small and did not appear to be clinically significant. Additionally, the administration of general anesthesia in this study makes detection of LAST and causality relationships challenging. Dr. Petit-Scott also noted that a single patient in the study had a bupivacaine $C_{\max}$ value greater than 1000 ng/mL noted 24 and 33 hours post-operatively. This patient experienced syncope five hours post-operatively, a time that did not correlate with the highest plasma concentration and felt to be unrelated.

Regarding HTX-011 400 mg/12 mg, there were three Phase 2 studies which evaluated the safety and efficacy of this dose. In Study HTX-011-209, patients undergoing TKA, there were no reported cases of LAST; however, of the studies which evaluated this dose, the TKA study reported the highest individual $C_{\max}$ values. Specifically, there were 10 patients with a $C_{\max}$ value greater than 1000 ng/mL, and 6 had $T_{\max}$ later than 24 hours post-operatively. In general, there did not appear to be an increased incidence in LAST-related adverse events in these 10 patients compared to patients with $C_{\max}$ values less than 1000 ng/mL. In Study HTX-011-C2015-203, patients undergoing complete abdominoplasty, there were no reported $C_{\max}$ values greater than 1000 ng/mL.

In Study HTX-011-211, patients undergoing bilateral augmentation mammoplasty, the highest mean $C_{\max}$ value was reported, 710 ng/mL, and there were five patients with $C_{\max}$ values greater than 1000 ng/mL, with the latest reported $T_{\max}$ (in these patients) 5.98 hours. There did not appear to be an increased incidence of LAST-related adverse events reported for these patients; however, there was one patient with a $C_{\max}$ value of 1360 ng/mL at 1.75 hours with dizziness, hypotension, and tremor. The dizziness and tremor may have been related to the bupivacaine concentration, but the hypotension was reported the next day, therefore unlikely related to the $C_{\max}$. In general, there was an increased incidence of the LAST-related adverse events of hypotension, dysgeusia, and bradycardia in HTX-011-treated patients compared to those treated with saline placebo or bupivacaine HCl. However, the highest incidence of LAST-related adverse events in this study were reported in the exploratory HTX-011 240 mg/7.2 mg treatment group, and not the HTX-011 400 mg/12 mg treatment group. It is worth reiterating that while the PK data from Study HTX-011-211 is included in the discussion regarding the maximum proposed HTX-011 dose, the data actually reflect divided and sequential HTX-011 200 mg/6 mg dosing.

In contrast to the findings reported in Dr. D'Agostino's pharmacology-toxicology review, there were no clinically significant changes in measured hematology parameters in patients treated with HTX-011. An in-depth review of white blood cell counts was performed by Dr. Petit-Scott during the initial review cycle given the concerns surrounding wound-related adverse events, and she did not identify clinically significant differences between treatment groups.

Regarding the cardiovascular and gastrointestinal (GI) risks associated with administration of NSAID-containing medications, Dr. Petit-Scott concluded that based on the low systemic meloxicam exposure after HTX-011 administration, the risk of CV or GI-related adverse events is low; however, the boxed warnings present in the Mobic® label are likely necessary for this NSAID-containing product.

In conclusion, the additional nonclinical information included in the NDA resubmission supports the systemic safety of HTX-011 400 mg/12 mg for the proposed clinical use, resulting in a favorable benefit:risk profile such that this dose can be approved for use in patients undergoing TKA.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The safety and efficacy of HTX-011 has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. An amended iPSP was submitted on July 19, 2019 with revised dates. The amended iPSP was agreed to on October 18, 2019.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues that need to be addressed during this review cycle. Refer to Dr. Petit-Scott's review for a discussion regarding financial disclosures and clinical site inspections.

12. Labeling

Consultations were obtained from the following Divisions:

- Division of Medication Error Prevention and Analysis (DMEPA)
- Division of Pediatric and Maternal Health (DPMH)

Their recommendations were considered and incorporated into the label.

Because this application is receiving a Complete Response, discussions with the Applicant regarding the text of the label will be conducted during the next review cycle. Extensive edits were made to the proposed label and included limited surgical site indications, revised route of administration language, inclusion of the NSAID boxed warnings, and updated clinical pharmacology information. Additionally, the proposed extended-release language will not be included in the label based on the lack of improved postsurgical analgesia in patients undergoing TKA following administration of HTX-011 compared to bupivacaine HCl.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action

Complete Response.

Benefit:Risk Assessment

As noted above, the Applicant has not adequately addressed the deficiencies discussed in the Complete Response Letter issued on April 30, 2019, including inadequate data to support exposure to excipients and drug product specifications, and the application is not approvable.

Post-Marketing Requirement

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. An amended iPSP was submitted on July 19, 2019, with justification supporting the amendment, and was agreed to on October 11, 2019. Heron cites ongoing bupivacaine shortages as a main reason for the amended protocol milestone dates. The proposed pediatric studies evaluating HTX-011 are as follows:

(b) (4)

Heron submitted a deferral request for all pediatric studies based on the adult studies complete and ready for approval and on the need for juvenile animal study results to inform clinical studies in pediatric patients under three years of age.

In addition, nonclinical PMRs will be required to support the studies in pediatric patients, as noted in the section below.

14. Comments to be sent to the Applicant

Based on the lack of adequate nonclinical data, I recommend a Complete Response Action for this application. The following deficiencies and information needed to correct them will be conveyed to the Applicant.

1. You have not provided adequate data to support your request for a waiver of reproductive and developmental studies for triacetin. Although you have concluded that the primary metabolites of triacetin do not represent a risk for reproductive and developmental effects, you have provided no data to support the conclusion that triacetin instilled into a wound at the maximum daily dose will not result in systemic exposure to the triacetin molecule. Provide data to support the conclusion that triacetin levels are not present in the systemic circulation via your drug product or conduct reproductive and developmental toxicology studies with triacetin via a route that mimics the clinical exposure to this excipient. If you elect to continue to rely upon the cited oral rat reproductive and developmental study, provide justification that the animals in that study were exposed to triacetin at levels comparable to those that will occur following clinical use of your drug product at the maximum recommended human dose.
2. You have not provided an adequate scientific bridge to the referenced oral reproductive and developmental studies submitted to qualify the safety of DMSO exposure via your drug product. Instillation of the drug product may result in higher C_{max} and AUC compared to oral studies and therefore it is not clear if the referenced studies adequately address the safety of your product. Provide data to support your conclusion that these referenced oral studies resulted in exposures to DMSO that exceed the exposure to DMSO via your drug product or conduct studies using an appropriate route of administration.
3. You have not provided adequate data to support the proposed drug product specification (b) (4) at NMT (b) (4)%. The nonclinical and clinical lots tested to date in your development program did not contain this high of a percentage (b) (4) and therefore does not qualify this specification. Further, you did not provide data to support your conclusion that (b) (4) would not contribute to the local tissue effects of the drug product. Either conduct a local tissue toxicity study that tests drug product that contains at least the maximum specified level (b) (4) reduce the specification (b) (4) to that which was tested in the

nonclinical toxicology studies, or provide data to support your hypothesis that the (b) (4) in the product does not contribute to local tissue effects of the drug product.

4. Your embryofetal development study in rabbits tested maleic acid via an oral route of administration rather than the proposed route of administration of your drug product and you did not provide an adequate scientific bridge to support your conclusion that the study provides adequate characterization of the developmental effects of maleic acid exposures via installation into a wound. Submit justification that the oral toxicology study resulted in exposures (C_{max} and AUC) that provide adequate coverage for the exposure via your drug product when the product is instilled into a wound. In addition, submit the final study report for the oral maleic acid embryofetal development study in the rabbit to the NDA.

The following additional nonclinical comments will be conveyed to the Applicant.

Although not listed as a deficiency in the first cycle, your proposed specification for DMSO of (b) (4) % has an upper limit that has never been tested in your clinical or nonclinical development program. As DMSO may contribute to local tissue toxicity, either revise the specification to reflect the testing completed by your development program, conduct a new study to characterize the local effects of your to-be-marketed drug product containing DMSO at the upper limit of your proposed specification, or justify why DMSO at (b) (4) % will not contribute to the local tissue effects of the drug product.

Once approved, the following PREA PMRs will be required:

1. Conduct a juvenile animal study in the rodent model to characterize the impact of DMSO on the developing brain to support clinical studies in pediatric patients under three years of age.
2. Conduct a juvenile animal study in an appropriate model to characterize the impact of meloxicam on the developing kidney, liver, lung, and testes to support clinical studies in pediatric patients under three years of age.

References

Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth & Analg.* 1989;69(5):563-9.

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/s/

RENEE L PETIT-SCOTT
06/26/2020 03:03:11 PM

MARTHA A VAN CLIEF
06/26/2020 03:05:43 PM

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06/26/2020 03:09:51 PM

Division Summary Review for Regulatory Action and Cross-Discipline Team Leader Review

Date	April 29, 2019
From	Martha A. Van Clief, MD; Rigoberto Roca, MD
Subject	Cross-Discipline Team Leader Review and Division Summary Review
NDA/BLA # and Supplement#	211988
Applicant	Heron Therapeutics, Inc.
Date of Original Submission	October 30, 2018
PDUFA Goal Date	April 30, 2019
Proprietary Name	Zynrelef™
Established or Proper Name	Bupivacaine and Meloxicam extended-release solution
Dosage Form	Solution
Applicant Proposed Indication/Population	(b) (4)
Applicant Proposed Dosing Regimen	400 mg bupivacaine and 12 mg meloxicam, single dose administration 200 mg bupivacaine and 9 mg meloxicam, single dose administration 60 mg bupivacaine and 1.8 mg meloxicam, single dose administration
Regulatory Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Renee Petit-Scott, MD
Statistical Review	Yan Zhou, PhD; Yi Ren, PhD; David Petullo, PhD
Pharmacology Toxicology Review	Jaime D'Agostino, PhD; Jay Chang, PhD; Dan Mellon, PhD
OPQ Review	Joe Leginus, PhD; Donna Christner, PhD; Venkat Pavuluri, PhD; Julia Pinto, PhD; Yoon Oh, PhD; Pei-I Chu, PhD; Christine Craig, PhD; Jonathan Swoboda, PhD; Hansong Chen, PharmD, PhD; Kelly Kitchens, PhD; Anika Lalmansingh, PhD; Venkateswara Pavuluri, PhD; Xiaofei Liu, PhD; Cindy Diem Ngo, PhD; Cynthia Sommers, PhD; Caryn McNab, PhD; Michael Tollon, PhD
CDRH	Florencia T. Wilson; Sarah Mollo; Capt. Alan M. Stevens
OSE/DMEPA	Jason Flint, MBA, PMP; Cameron Johnson, PharmD; Otto L. Townsend, PharmD; Quynh Nhu Nguyen, MS
DPMH	Christos Mastroyannis, MD; Tamara Johnson, MD, MS; Lynne P. Yao, MD
IRT-QT	Girish K. Bende; Janell E. Chen; Dalong Huang; Mohammad A. Rahman; Michael Y. Li; Jose Vincente Ruiz; Lars Johannesen; Christine E. Garnett
Clinical Pharmacology	Suresh B. Narahariseti, PhD; Michael Bewernitz, PhD; Keven Krudys, PhD
OSI/DCCE/GCPAB	John Lee, MD; Phillip Kronstein, MD; Kassa Ayalew MD, MPH

CDTL = Cross-Discipline Team Leader
CDRH = Center for Devices and Radiological Health
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
OND = Office of New Drugs

OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology
IRT-QT = Interdisciplinary Review Team for QT Studies
OSI = Office of Scientific Investigations
DCCE = Division of Clinical Compliance Evaluations
GCPAB = Good Clinical Practice Assessment Branch

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

HTX-011, developed by Heron Therapeutics, Inc, is a formulation of bupivacaine and meloxicam in a Biochronomer® vehicle to allow an extended release profile of the drug product beyond that currently available by immediate release local anesthetics. The proposed indication for HTX-011 is for (b) (4) HTX-011 is a fixed-dose combination product and a co-packaged combination drug-device products. The regulatory action for HTX-011 is Complete Response based upon CMC and Pharmacology/Toxicology deficiencies.

Postoperative pain is a serious condition, based upon the extent of tissue injury during the surgical procedure and the extent of rehabilitation that is required for the patient to resume activities of daily living. Current treatment options include the use of local anesthetics by infiltration or via nerve blocks, opioids, non-opioid analgesics, and multimodal therapy which includes the administration of 2 or more drugs that act by different mechanisms for providing analgesia with the intent of improved pain relief while reducing opioid requirements and opioid-related adverse events. The standard of care for many surgical procedures is the use of local anesthetic infiltration, nerve blocks, or infusion via indwelling catheters combined with non-opioid analgesics, and opioids. The limitation of the currently available local anesthetics is the short duration of immediate release local anesthetics.

The results of the HTX-011 drug development program support an analgesic benefit over saline placebo and bupivacaine HCl wound infiltration for up to 72 hours post-operatively after bunionectomy, Study HTX-011-301 (Study 301) with HTX-011 60 mg/1.8 mg; and open unilateral inguinal hernia repair (IHR or herniorrhaphy) with mesh, Study HTX-011-302 (Study 302) with HTX-011 300 mg/9 mg. The results of the primary endpoint, Mean area AUC of the NRS-R pain intensity scores through 48 hours (AUC₀₋₄₈) for both HTX-011 treatment groups compared with saline placebo and the key secondary efficacy endpoint, Mean AUC₀₋₇₂ for both HTX-011 treatment groups compared with bupivacaine HCl, from the Phase 3 studies are statistically, as well as clinically, significant, (b) (4)

When administered to patients undergoing a bunionectomy or an open IHR with mesh, the clinical risks of HTX-011 include local anesthetic systemic toxicity (LAST), cardiovascular and gastrointestinal adverse events as described in the Mobic® label boxed warnings, and impaired healing of the surgical wound.

In general, there did not appear to be any patients in the Phase 3 studies who experienced a clinically significant episode of LAST. The reported mean maximum concentration, C_{max}, for bupivacaine after administration of HTX-011 60 mg/1.8 mg in patients undergoing bunionectomy was

33 ng/mL with a mean T_{max} of 3 hours. The mean C_{max} for bupivacaine after administration of HTX-011 300 mg/9 mg in patients undergoing open IHR with mesh was 271 ng/mL with a mean T_{max} of 18 hours. There was a single patient in Study 302 with a C_{max} greater than 1000 ng/mL (measured 1290 ng/mL at 24 hours, estimated 1310 ng/mL at 33 hours). This patient had a single potential LAST-related adverse event of syncope, moderate in severity, approximately five hours after study drug administration. The investigator felt the adverse event was unlikely related to study drug administration, which appears a reasonable conclusion since symptoms did not occur at C_{max} . The incidence of LAST-related adverse events appeared to be similar in the bupivacaine HCl treatment group compared to the HTX-011 treatment group.

Regarding the need for the boxed warnings included in the Mobic® label, the risk for development of cardiovascular (CV) thrombotic and gastrointestinal (GI) bleeding, ulceration, or perforation events after a single administration of HTX-011 is low due to the lower systemic exposure compared to repeated oral meloxicam administration. Specifically, the Mobic® package insert states that C_{max} after oral administration of 7.5 mg was 1050 ng/mL. The mean area under the curve to infinity (AUC_{inf}) was calculated for Mobic® based on clearance values identified in the label and determined to be 85227 ng·h/mL for three days and 142045 ng·h/mL for five days. The maximum dose that will be approved is HTX-011 300 mg/9 mg, for use during open IHR with mesh. The measured PK parameters for that dose were reported as C_{max} 196 ng/mL and AUC_{inf} 21300 ng·h/mL, values much lower than those observed after oral Mobic® administration. Additionally, review of the observed adverse events across drug development did not identify a single case of a CV thrombotic event or a GI bleed, ulceration, or perforation. These results are reassuring and support the safe use of HTX-011 for the indicated surgical procedures. However, all NSAID-containing products must include the boxed warnings in the label, and it is not clear if there is a level of exposure that would negate the risk and eliminate the need for the boxed warnings in the label.

The risk of impaired or delayed healing of the surgical wound after treatment with HTX-011 was extensively evaluated during review of the NDA. There was a measurable increase in wound-related adverse events, such as incision site cellulitis, infection, and impaired healing, after administration of HTX-011 60 mg/1.8 mg during bunionectomy compared to saline placebo and bupivacaine HCl. However, the finding of wound-related adverse events does not preclude the approval of HTX-011 for the following three reasons. First, the majority of reported wound-related adverse events were mild in severity and resolved by Day 42, the end of the study. Second, the soft tissue wound changes did not result in more clinically significant bony changes, such as osteomyelitis or failure of the hardware, as assessed by post-operative x-rays. And third, smaller incisions and surgical spaces may not have been able to accommodate the entire volume of HTX-011 (2.1 mL), resulting in leakage of excess medication from the wound, and potentially poor approximation of the wound edges, local inflammation, and delayed healing. Furthermore, there did not appear to be an increase in wound-related adverse events reported during Study 302, IHR with mesh.

The clinical benefits of HTX-011 administration during bunionectomy and IHR with mesh outweigh the clinical risks discussed and include a safe and novel route of administration, extended duration of postsurgical analgesia, and an additional analgesic treatment option. The proposed route of HTX-011 administration is instillation into the surgical wound via a needleless Luer lock syringe with unique applicator. The lack of injection, with a needle, obviates the risk of inadvertent intravascular administration, thereby increasing the margin of safety of this bupivacaine-based product beyond what is observed during injection of immediate release bupivacaine HCl. Intravascular and systemic absorption, however, is still a concern in the setting of large doses or use in areas of increased vascularity, but a narrowed postsurgical indication and limitations of use

statement(s) can mitigate this risk.

HTX-011 has demonstrated safe and efficacious post-operative analgesia after bunionectomy and open IHR with mesh for up to 72 hours, a clear clinical benefit beyond immediate-release bupivacaine HCl wound infiltration. Additionally, there were statistically, and clinically, significant decreases in opioid analgesic use in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine HCl. A final benefit of HTX-011 is that it will offer clinicians an additional treatment option in the management of acute postsurgical pain after bunionectomy and open inguinal hernia repair with mesh, both of which are common surgical procedures, with the potential to have a positive impact on a large number of patient outcomes.

However, based on evaluation of information provided in the NDA original submission with subsequent amendments to date (SN#0002 to #0035) and the recent pre-approval inspection of drug product manufacturing facilities (b) (4) NDA 211988 for HTX-011 (bupivacaine and meloxicam) is NOT APPROVABLE from quality (CMC) and a Pharmacology/Toxicology perspective based on the following deficiencies.

1. Leachables study data is inadequate to support the proposed shelf-life of the drug product. In addition, the lack of adequate study data prevents a definitive toxicological risk assessment, thus the CMC deficiency has pharmacology toxicology implications.
2. Sterility assurance of the syringe tip cap was established at release and through the end of shelf-life of the component approved under 510(k).
3. Deficiencies identified in facility inspection for (b) (4) (FEI: (b) (4)) manufacturing facility.

Therefore, HTX-011 will receive a Complete Response based on the CMC and Pharmacology/Toxicology deficiencies.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Acute pain is a normal response to a surgical procedure, due tissue trauma. Postsurgical pain can be self-limiting and may often only requires short term treatment. However, the duration of treatment may vary depending on the specific surgical procedure. - Inadequate management of postsurgical pain is a serious condition and may result in delayed recovery, ineffective rehabilitation, and extended hospitalization.	Effective management of acute postsurgical pain is essential to prevent the development of postsurgical complications, chronic pain conditions, and opioid use disorder.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Patients that are not adequately treated may develop postsurgical complications, such as, pneumonia, deep venous thrombosis, infection, or delayed healing. • Poor management of acute postsurgical pain may lead to the development of a chronic pain condition. The transition to chronic pain is complex and not completely understood, however, it appears that biological mechanisms are involved including neuroplasticity, pain modulation, and central sensitization. • Chronic pain leads to emotional suffering and increased financial expenses, to include, direct healthcare costs, absenteeism, lost productivity and the need for social services support.	
Current Treatment Options	• Current treatment options for postsurgical pain include the following: – opioid analgesics – non-opioid analgesics – local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia • Opioid analgesics are first-line therapy for post -surgical pain. However, they are associated with undesirable side effects, such as, sedation, nausea, vomiting, and constipation. • The use of opioid for postsurgical pain may lead to long-term use and abuse. Studies have reported that an opioid-naïve patient who receives an opioid prescription within 7 days of a low-risk surgery were 44% more likely to become long-term opioid users within one year compared with those that did not receive a prescription. • Non-opioids alone are usually not adequate for postsurgical analgesia. More often they are use as adjuncts for postsurgical pain to reduce the need for opioid analgesics. • The use of local anesthetics via infiltration or nerve block is preferred, when applicable, because their use may eliminate the need for potent opioids. However, the limitation of local anesthetics is their duration of action of 8 to 12 hours after surgery, thus, requiring the use of potent opioids to manage postsurgical pain.	The current treatments for postsurgical analgesia have serious drawbacks. • Opioids have undesirable side effects and their use may lead to opioid abuse disorder. • Non-opioids are not adequate to manage postsurgical analgesia except for minor procedures. • Local anesthetics are effective but are limited by their short duration of action that does not meet the need for several days to a week of analgesia. Extended-release formulations of local anesthetics may address an unmet need if the duration of analgesia can extend to cover the period of moderate to severe postsurgical pain. While there are several marketed, approved

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. Ropivacaine and bupivacaine are considered longer-acting than lidocaine and generally provide up to eight hours of postsurgical pain relief when administered via wound infiltration. • There are currently no approved local anesthetics with an extended release or slow release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a dilute concentration of bupivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to prolong the duration of action of immediate release bupivacaine.	bupivacaine products for use in the management of postsurgical pain, none have an extended release profile that reliably prolongs postsurgical analgesia beyond that observed after administration of immediate release bupivacaine.
Benefit	• The applicant conducted two Phase 3 studies HTX-011-301(Study 301) in bunionectomy and HTX-011-302 (Study 302) in inguinal herniorrhaphy with mesh. The two studies were similarly designed as placebo and active-controlled (bupivacaine HCl) studies in adult patients with acute postsurgical pain. • The study population were adult patients undergoing either unilateral bunionectomy (Study 301) or unilateral inguinal herniorrhaphy with mesh (Study 302). • The primary efficacy endpoint was the mean AUC of the NRS-A of pain intensity scores through 72h (AUC₀₋₇₂) for HTX-011 compared with PBO which is the preferred endpoint for studies in postoperative pain. The Applicant met statistical significance for the primary endpoint. • The key secondary efficacy endpoints were: – 1st key secondary efficacy endpoint – Mean AUC₀₋₇₂ of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl ▪ The Division recommended to the Applicant during their drug development program to include an active comparator, specifically bupivacaine. The Applicant met	The Phase 3 studies meet the evidentiary standard, because placebo-controlled trials are considered acceptable for an adequate and well-controlled study [21 CFR 314.126]. Approval of HTX-011 would offer clinicians an additional bupivacaine product to administer for postsurgical pain management after bunionectomy and open inguinal herniorrhaphy. Additionally, HTX-011 is an extended-release product resulting in post-operative analgesia through 72 hours. The Phase 3 clinical studies conducted by the Applicant included a bupivacaine control treatment group, such that the efficacy and safety comparisons allowed a more relevant assessment of the true clinical benefit of HTX-011 over standard of care bupivacaine wound infiltration.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	statistical significance for this endpoint. – 2nd key secondary efficacy endpoint – Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo – 3rd key secondary efficacy endpoint – proportion of patients who are opioid-free through 72 hours for HTX-011 compared to bupivacaine HCl – 4th key secondary efficacy endpoint – Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl. ▪ The 2nd, 3rd, and 4th key efficacy endpoints are important because the intent of extended-release local anesthetics is to reduce the opioid use postoperatively. The Applicant was able to show a reduction in opioid use after use of HTX-011 for postoperative analgesia. • Bupivacaine has been used for decades in the treatment of postsurgical pain when administered for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia/analgesia. It is an effective local anesthetic with a well-established safety profile. • For soft tissue surgical procedures, bupivacaine is most commonly administered via wound infiltration, which reduces postsurgical pain for a short period of time, generally up to six hours. For orthopedic procedures, bupivacaine is also administered via wound infiltration, in addition to its use as a regional anesthetic for peripheral nerve blockade and neuraxial anesthesia. Depending on the technique, postsurgical analgesia can last for several hours or days, if necessary. • Meloxicam is an orally administered NSAID indicated once daily for the treatment of a variety of arthritic conditions. Like other NSAID medications, orally administered meloxicam inhibits cyclooxygenase enzymes (COX-1 and COX-2), resulting in decreased production of inflammatory prostaglandins and ultimately analgesia. The mechanism of action of action when administered locally in HTX-011	There was a statistically significant decrease in post-operative opioid analgesic use through 72 hours in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine. However, it appears that the largest difference in opioid use between treatment groups was early in the post-operative period, i.e., < 24 hours, which likely contributed to the persistent statistical significance through 72 hours. There was a trend toward a lower incidence of opioid-related adverse events in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine; however, review of concomitant medications indicated less impressive differences in the treatment of opioid-related adverse events, such as post-operative nausea and vomiting. Furthermore, there were three confounding variables that impacted the clinical significance of the reported opioid-related adverse events. First, because all patients received concomitant sedation (Study 301) or general anesthesia (Study 302) during the evaluated procedures, interpretation of the data is challenging. Second, it does not appear the study protocols stratified patients with a history of post-operative nausea and vomiting. And lastly, patient factors, such as gender and smoking history, impact the incidence of post-operative nausea and vomiting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	is not completely understood, but may involve two separate mechanisms. First, it may act locally as an anti-inflammatory, thereby decreasing tissue swelling and pain. This seems less likely given the results of nonclinical studies, indicating an increase in local tissue inflammation after administration of HTX-011. The second possible mechanism, and the one the Applicant proposes, is based on the maintenance of physiologic pH in the setting of tissue injury, thereby allowing more nonionized bupivacaine to penetrate nerves and inhibit conduction of sensory information. While this is possible, nonclinical data indicate that during the 24 hours of reported maximum meloxicam release, there is not a large difference in tissue pH between animals treated with HTX-011 and those treated with placebo. • The Applicant has demonstrated the improved clinical benefit of HTX-011 compared to treatment with bupivacaine (the disease-active ingredient) and meloxicam individually in the Biochronomer® vehicle after bunionectomy and open inguinal herniorrhaphy. • Well-controlled post-operative pain results in the following: – Improved patient outcomes, including decrease length of hospital stay – Improved patient satisfaction, which may translate into reimbursement assurances – Less time lost from work and school – Ability to perform procedures on an out-patient basis – Improved mobility and ambulation, and less time for return to baseline function, depending on the procedure performed – Potential decreased health care cost and burden due to short-term disability	The totality of the impact of adequate postsurgical pain management on health care outcomes is likely immeasurable and the benefits are likely to extend beyond individual patient outcomes, potentially impacting overall cost and societal burden of poorly managed pain.
Risk and Risk Management	The safety database in the drug development program consisted of 448 patients that received the intended commercial formulation of HTX-011 via the intended route of administration, currently described as instillation using a unique applicator without a needle.	Despite the higher dose of bupivacaine administered in HTX-011 300 mg/9 mg than is currently approved in the Marcaine™ label, the risk of developing LAST appears low. In general, the maximum systemic

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The three safety issues of greatest concern with administration of HTX-011 include the development of LAST, CV thrombosis and GI-related adverse events as described in the Mobic® label boxed warnings, and impaired healing of the surgical wound. <u>LAST</u> - Factors influencing the development of LAST include the site of administration and total dose administered. The proposed maximum dose of bupivacaine in HTX-011 300 mg/9 mg is higher than the recommend dose in the Marcaine™ product label, 175 mg without epinephrine. Use of a higher than currently recommended dose may lead to increased incidence of LAST depending on the surgical location, specifically the vascularity of the surrounding tissue. - Because the PK profile of HTX-011 is variable in the surgical populations evaluated, use of the product in other surgical models or for other painful conditions is not recommended without further studies on new surgical models. While bupivacaine has a long history of clinical use and the safety profile is well-established, it is highly cardiotoxic due to its strong affinity for cardiac Na⁺ channels and the high degree of protein binding. Systemic exposure to increased amounts of bupivacaine poses the greatest risk for the development of toxicity and HTX-011 instillation into highly vascular sites is likely to increase the risk above what has been characterized in the Applicant's Phase 3 clinical studies. - An additional concern regarding the variable PK profile of HTX-011 is the likelihood of patients being in an unmonitored setting around C_{max}, a time when the risk of toxicity is the highest. This can potentially be mitigated by adequate and comprehensive patient education regarding the signs and symptoms associated with bupivacaine toxicity. <u>CV Thrombosis</u>	exposure after administration of HTX-011 300 mg/9 mg was below the threshold, 1000 to 2000 ng/mL, for local anesthetic-induced neurotoxicity. There was a single patient in Study 302 with a serum concentration greater than 1000 ng/mL. The patient did experience a potential LAST-related adverse event, syncope 5 hours after HTX-011 administration and did not have any further symptoms when the serum concentration exceeded 1000 ng/mL. . Therefore, it is appears unlikely that this event was associated with LAST. In the Phase 3 clinical studies, there did not appear to be any cases of clinically significant LAST and the incidence of potential LAST-related treatment-emergent adverse events was similar between the HTX-011 and bupivacaine HCl treatment groups. The preferred terms that were reported with an increased incidence in the HTX-011 treatment group in Study 302 included the following: hypotension, muscle twitching, paresthesia oral, and sinus arrhythmia. The difference between treatment groups for these preferred terms was less than 1%, suggesting the difference in incidence is not clinically relevant or significant. The development of LAST with use of this drug product can be mitigated by the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- NSAID use and the resulting inhibition of the cyclooxygenase enzymes has been linked to CV thrombotic events, including myocardial infarction (MI) and graft stenosis after coronary artery bypass graft surgery. Because meloxicam is an NSAID, oral administration can result in a CV thrombotic event and the product label includes the boxed warnings required for NSAID medications. - There were no reported adverse events related to CV-thrombosis. The single patient death in Study 301 on Day 17 may have been related to underlying cardiac disease, however, this was a patient in the bupivacaine HCl treatment group. - In Study 302, there were no clinically meaningful differences between treatment groups in mean or mean change from baseline for heart rate, PR or RR interval, or QRS duration. Additionally, there did not appear to be clinically meaningful differences between treatment groups in the QT or QTcF intervals and the highest post-baseline QTcF was also similar. - Despite the lack of a demonstrable risk with HTX-011 administration in combination with the overall lower systemic meloxicam exposure, the CV thrombosis boxed warnings are likely required for the HTX-011 product label. <u>GI Bleeding, Ulceration, and Perforation</u> - Similar to the CV thrombosis adverse events, NSAID use has been linked to GI-related adverse events including bleeding, ulceration, and perforation of the stomach or intestines. Because meloxicam is an NSAID, oral administration can result in these adverse events and the product label includes the boxed warnings required for NSAID medications. - There were no reported adverse events related to GI bleeding, ulceration, or perforation. The adverse event preferred terms in the Gastrointestinal Disorders System Organ Class (SOC) that were most commonly reported in Study 302 included nausea, constipation, and vomiting.	following: Narrow postsurgical indication, based on safety data captured from adequate and well-controlled Phase 3 studies Avoid administration in highly vascular surgical sites (e.g., intrathoracic) or procedures (e.g., multilevel spinal fusion with instrumentation) Avoid administration on denuded tissues, such as burns Maximum recommended dose 300 mg/9 mg The proposed route of administration of HTX-011 offers a margin of safety that other injectable bupivacaine-containing products do not. Specifically, because HTX-011 is administered via needless Luer lock syringe, the risk of inadvertent intravascular injection, and hence catastrophic LAST, is low. While there were no reported adverse events concerning for CV thrombosis or GI-related adverse events after administration of HTX-011 and the overall systemic meloxicam exposure is lower than that observed after oral administration, it is not clear if there is a level of exposure that would negate the risk and eliminate the need for the boxed warnings in the label. Therefore, the NSAID boxed warnings are required in the HTX-011 label.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Despite the lack of a demonstrable risk with HTX-011 administration in combination with the overall lower systemic meloxicam exposure, the GI-related adverse event boxed warnings are likely required for the HTX-011 product label. <u>Surgical Wound Healing</u> - An extensive review of surgical wound healing data indicated that there is an increase in wound-related adverse events in patients treated with HTX-011 after certain surgical procedures, specifically bunionectomy and abdominoplasty. - Bunionectomy: - In Study 301, the adverse events with the highest incidence across all treatment groups included incision site oedema (sic), erythema, and impaired healing. In general, the HTX-011 treatment group had approximately 1% to 3% higher incidence of these adverse events. - For the more clinically significant adverse events of incision site cellulitis and wound dehiscence, the HTX-011 treatment group had approximately 2% to 3% higher incidence. - The cause of these wound-related adverse events is not fully understood and may be due to an excipient in the Biochronomer® formulation (b) (4). Leakage of excess HTX-011 from the small bunionectomy wound, resulting in local inflammation, as proposed by the Applicant, is also a reasonable possibility. - Inguinal herniorrhaphy with mesh: - There did not appear to be an increase in wound-related adverse events reported during Study 302, IHR with mesh. - However, based on evaluation of information provided in the NDA original submission with subsequent amendments to date (SN#0002 to #0035) and the recent pre-approval inspection of drug product manufacturing facilities (b) (4) NDA 211988 for HTX-011 (bupivacaine and	The majority of wound-related adverse events reported during Study 301 were graded as mild in severity and resolved by Day 42, the end of the study. The incidence of adverse events related to bone healing or hardware failure was similar across treatment groups. Specifically, there were a total of seven patients with either mal-union or delayed bone healing as identified in post-operative x-rays. Three patients in the HTX-011 treatment group experienced mal-union; two were thought to be due to poor compliance with post-operative care and one was due to trauma. Four patients had delayed bone healing; one each in the HTX-011 and saline placebo treatment groups and two in the bupivacaine HCl treatment group. A possible explanation for the increased incidence of wound-related adverse events in patients undergoing bunionectomy is that excess HTX-011 leakage from the small surgical wound may have resulted in poor approximation of the wound edges, local inflammation, and delayed soft tissue healing. A possible explanation for the increased incidence of wound dehiscence in patients undergoing complete abdominoplasty (in the HTX-011 300 mg/9 mg combination administration treatment group) may be due to the injection route of administration. Specifically, multiple injections of a viscous liquid into the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	meloxicam) is NOT APPROVABLE from quality (CMC) and a Pharmacology/Toxicology perspective based on the following deficiencies. – Leachables study data is inadequate to support the proposed shelf-life of the drug product. In addition, the lack of adequate study data prevents a definitive toxicological risk assessment, thus the CMC deficiency has pharmacology toxicology implications. – Sterility assurance of the syringe tip cap was established at release and through the end of shelf-life of the component approved under 510(k). – Deficiencies identified in facility inspection for (b) (4) (FEI: (b) (4)) manufacturing facility.	posterior rectus sheath plication may have disrupted the repair and ultimately adversely impact wound healing. Mitigation strategies to minimize the wound-related adverse events that will be included in the product label include the following (final language to be determined): • Avoid excess HTX-011 administration; i.e., instill only as much volume as the surgical space will accommodate • Ensure complete closure of the surgical wound and approximation of the wound edges • Only administer HTX-011 during surgical procedures for which the safety and efficacy has been thoroughly evaluated. However, based upon the CMC and Pharmacology/Toxicology deficiencies NDA 211988 for HTX-011 will receive a Complete Response.

2. Introduction and Background

This document will serve as the Cross-Discipline Team Leader (CDTL) review of this new drug application (NDA), as well as the Division Summary (DD) review for the decision on the regulatory action.

The Applicant, Heron Pharmaceuticals, Inc., has submitted a new drug application (NDA) for Zynrelef™, a bupivacaine and meloxicam extended-release solution. The Applicant is proposing to rely on the Agency's finding of efficacy and safety for Marcaine™ (NDA 016964) and Mobic® (NDA 020938); therefore, this submission is a 505 (b)(2) submission. The current indication for Marcaine™ is "for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures" (Marcaine™ product label, 2018). The indication for Mobic® is for osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis in patient who weigh ≥ 60 kg (Mobic® product label, 2018).

This document will capture the final outcomes of any items that were still under discussion at the time Dr. Petit-Scott's review was finalized.

As noted in Dr. Petit-Scott's review, Zynrelef™ is a formulation of bupivacaine and meloxicam in a Biochronomer® vehicle. The intent of the Biochronomer® vehicle is to extend the duration of action of bupivacaine such that post-operative opioid analgesic use and, therefore, opioid-related adverse events are reduced. The Applicant's proposed indication is (b) (4)

Bupivacaine HCl is an amide local anesthetic and local anesthetics block the generation and conduction of nerve impulses, thereby, producing local anesthesia and analgesia. The proposed dosing regimen for Zynrelef™ is one of the following based upon the size of the surgical incision:

- 400 mg bupivacaine and 12 mg meloxicam, 20 mL single-dose glass vial
- 200 mg bupivacaine and 9 mg meloxicam, 10 mL single-dose glass vial
- 60 mg bupivacaine and 1.8 mg meloxicam, 10 mL single-dose glass vial

The regulatory history and interactions are well-summarized in Dr. Petit-Scott's review. Heron Therapeutics, Inc., submitted IND 125927 in May 2015, for evaluation of HTX-011, bupivacaine and meloxicam extended release solution (b) (4)

(b) (4) The following table, reproduced from Dr. Petit-Scott's review, is a high-level summary of the key interactions between Heron Therapeutics, Inc. and the Agency regarding the clinical development program.

Summary of Pre-Submission and Submission Regulatory Activities

Meeting/Communication/Date	Event/Key Clinical Issues
IND 125927 submitted / May 7, 2015	Study HTX-011-C2015-201 allowed to proceed / June 14, 2015
End of Phase 2 (EOP2) Meeting / June 15, 2017	The major clinical topics for discussion during the EOP2 meeting were as follows: – Primary, key secondary, other secondary, and exploratory efficacy endpoints – (b) (4) indication – Reduced need for postoperative opioid analgesics – Active versus placebo control – Requirements for a superiority claim over active control – Method of administration of HTX-011 – Phase 2b efficacy results and their possible inclusion in the label – Evaluation of bupivacaine as the disease-active ingredient – Safety database – Human Factors study – Convenience kit and co-packaging of the drug and device
Initial Pediatric Study Plan (iPSP) Received/August 13, 2017	Written feedback in the form of a tracked-changes document was sent to the Sponsor.
Fast Track Designation / October 24, 2017	The preliminary data for the to-be-marketed formulation of HTX-011 treats a serious condition and appears to demonstrate the potential to address an unmet clinical need.
Type C Meeting / April 3, 2018	The major clinical topics for discussion during this Type C meeting were as follows: – Necessary scientific bridge for HTX-011 and Mobic (referenced Advisory Committee meeting material for Exparel) – Renal impairment study likely not needed based on the active moieties in HTX-011 – (b) (4) plasma concentrations and patients with renal impairment – Measuring the bupivacaine metabolite PPX is not required – Both C_{max} and AUC will be used for systemic exposure comparisons of HTX-011 to Marcaine – The PK profile and administration technique do not reduce the risk of LAST alone – Acceptability of a thorough QT evaluation waiver – PK profiles are needed for every route of administration studied – Acceptability of the ISE in Module 2 – Route of administration

Meeting/Communication/Date	Event/Key Clinical Issues
Breakthrough Therapy Designation / June 14, 2018	Based on preliminary data from two Phase 3 clinical studies, demonstrating a significant improvement over the current standard-of-care, bupivacaine HCl, in both pain intensity scores and duration of pain control.
Pre-NDA Meeting / June 20, 2018	The major clinical topics for discussion during the Pre-NDA meeting were as follows: – Necessary PK data to establish a scientific bridge – Highly vascular surgical sites include the thoracic cavity, head and neck procedures, and large spine procedures – Possible Advisory Committee Meeting – The PK profile of HTX-011 does not demonstrate a consistent, predictable PK profile (Phase 2 study results)
Rolling Review Request / August 30, 2018	As discussed during the Pre-NDA meeting, a formal request for a proposed Rolling Review was submitted.
Rolling Review Granted / September 12, 2018	No additional advice provided.
Agreed Initial Pediatric Study Plan (iPSP) / September 27, 2018	No additional advice provided.
NDA 211988 Submission (clinical data) / Oct. 30, 2018	NDA received.
NDA 211988 Filed / December 28, 2018	Potential clinical review issues include the following: – The maximum recommended HTX-011 labeled dosing, 400 mg/12 mg, was not evaluated in the pivotal Phase 3 studies. – The impact of HTX-011 on wound healing. – The clinical significance of the reported adverse event (preferred term) “skin odour abnormal”. – Dosing recommendations based on the size of the surgical site. – Clarification of the route of administration. – Acceptability of omission of the boxed warning for meloxicam regarding gastrointestinal and cardiovascular risks.

Source: Dr. Petit-Scott’s Clinical Review

3. Product Quality

The following is adapted from the Office of Product Quality (OPQ) Quality Assessment Review:

The **drug product review team** concluded the following:

The limited data provided on leachables in the drug product, particularly (b) (4) identified in study 3 is not adequate to assure that the leachables remain within permitted daily exposure limits through the end of shelf-life.

The **Facility reviewer (OPF)** investigator conveyed deficiencies to the representative of the facility, (b) (4) (FEI: (b) (4)) manufacturing facility during inspection for this application.

The **CDRH reviewer** from the **Center for Devices and Radiological Health (CDRH)** concluded the following: The Applicant did not provide adequate information to ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life.

The review team identified other deficiencies which were not considered approvability issues. For additional details, please refer to the OPQ review.

Recommendation and Conclusion on Approvability (verbatim from the Quality Review Assessment):

Based on evaluation of quality information provided in the NDA original submission with subsequent amendments to date (SN#0002 to #0035) and the recent pre-approval inspection of drug product manufacturing facilities (b) (4) **NDA 211988 for ZYNRELEF™ (bupivacaine and meloxicam) Extended-release solution is NOT APPROVABLE** from quality (CMC) perspective. The deficiencies are outlined below.

1. Leachables study data is inadequate to support the proposed shelf-life of the drug product.
2. Sterility assurance of the syringe tip cap was established at release and through the end of shelf-life of the component approved under 510(k).
3. Deficiencies identified in facility inspection for (b) (4) (FEI: (b) (4)) manufacturing facility.

I concur with the conclusion of the OPQ team.

4. Nonclinical Pharmacology/Toxicology

The following findings are adapted from Dr. D'Agostino's Review.

1. The Applicant has not provided adequate data to support the safety of the DMSO or triacetin in the drug product. Therefore, the impact of these two excipients on the standard reproductive and developmental battery of studies is not adequately described.
2. The Applicant's toxicological risk assessment for the excipient maleic acid does not address the potential impact of maleic acid on embryo-fetal development in a second species (typically rabbit).
3. The Applicant has not provided adequate data to qualify the proposed drug product degradant (b) (4) which exceeds the ICH Q3B(R2) qualification threshold.
4. The Applicant did not provide adequate data to support the safety of the drug product specification (b) (4)

5. The Applicant did not provided adequate leachable data to permit substantive toxicological evaluation of the safety of the container closure system (b) (4) (b) (4) for this drug product.
6. The current nonclinical data appears to support the safety of bupivacaine when the product is dosed up to 300 mg of bupivacaine, however, the data do not appear to provide adequate coverage for the maximum AUC_{0-24h} via this drug product at the Applicant's proposed maximum dose of 400 mg bupivacaine.

The following information concerning carcinogenicity and reproductive and developmental toxicity is adapted from Dr. D'Agostino's review.

Carcinogenicity studies with HTX-011 are not required for an acute-use drug.

No reproductive and developmental toxicity studies were conducted with HTX-011. The Applicant is relying upon the Agency previous finding of safety of bupivacaine and meloxicam via the 505(b)(2) pathway. The labeling will reflect the existing data in the referenced labels adjusted for dose.

The following is the final recommendation of the pharmacology/toxicology team from Dr. D'Agostino's review:

The Applicant has not submitted adequate extractable/leachable testing in order to assure the safety of potential leachables from the container closure (b) (4) (b) (4). Technically the design of the extractable leachable testing is a CMC deficiency. However, lack of adequate studies prevents a definitive toxicological risk assessment, thus the CMC deficiency has pharmacology toxicology implications.

I concur with the review team that there are non-clinical deficiencies that preclude the approval of this NDA.

5. Clinical Pharmacology

As noted in Dr. Narahariseti's review, the clinical program for HTX-011 consisted of Phase 2 and Phase 3 clinical studies in surgical procedures, with PK sampling as shown in the following table.

Clinical studies of HTX-011 in surgical procedures with PK sampling

Study (Phase)	Surgical Procedure	Dose (N) and administration procedure		Type and duration of PK sampling
		HTX-011 (bupivacaine/meloxicam)	Bupivacaine HCl	
Study 202 (P2)	Herniorrhaphy	300 mg/ 9 mg (N=16); Instillation plus, fentanyl 50 mcg IV	75 mg (0.25%) (N=17); Infiltration injection plus, fentanyl 50 mcg IV	Full PK, 120 h
Study 208 (P2)	Bunionectomy	60 mg/ 1.8 mg (N=17); Instillation	50 mg (0.5%) (N=25); Infiltration injection (with or without using Mayo block)	Full PK, 120 h
Study 211 (P2)	Augmentation Mammoplasty	400 mg/ 12 mg (N=49); Instillation	50 mg (0.25%) (N=41); Nerve block	Full PK, 120 h
Study 209 (P2)	Total Knee Arthroplasty	400 mg/ 12 mg (N=53); Instillation	125 mg (0.25%) (N=65); Injection	Full PK, 240 h
Study 203 (P2)	Complete Abdominoplasty	400 mg/ 12 mg (N=17); Instillation	100 mg (0.25%); (N=17, Part C) Infiltration injection	Full PK, 120 h
Study 302 (P3)	Herniorrhaphy	300 mg/ 9 mg (N=161); Instillation	75 mg (0.25%); Injection	Population-PK * (4 samples)
Study 301 (P3)	Bunionectomy	60 mg/ 1.8 mg (N=157); Instillation	50 mg (0.5%); Injection	Population-PK * (4 samples)

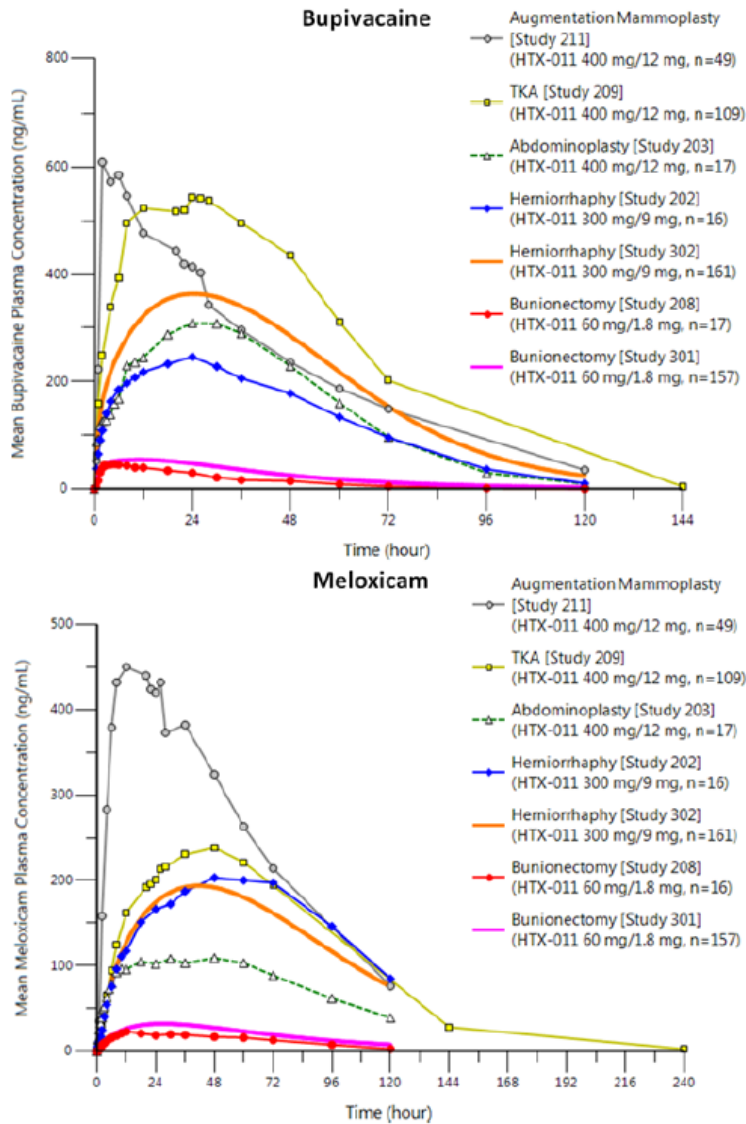
Source: Dr. Narahariseti's review

The following is adapted from Dr. Narahariseti's review.

In all clinical studies, reference drug, bupivacaine HCl was administered as a separate treatment arm. For Phase 2 studies, for both HTX-011 and bupivacaine HCl, full PK sampling from 0 to 120 h, except for Study 209, where it was 0 to 240 h, was conducted. For Phase 3 studies, HTX-011 and bupivacaine HCl had population-PK sampling with 4 samples collected from each subject.

The PK profiles and PK parameters of bupivacaine and meloxicam following single dose HTX-011 (bupivacaine/meloxicam) administered by instillation in each surgical procedure are shown in the figure below. The graphs demonstrate the variability of the PK parameters for bupivacaine and meloxicam for the same administered dose of HTX-011 in different surgical procedures.

Mean Bupivacaine and Meloxicam Plasma Concentrations Versus Time Profiles Following Instillation of HTX-011 in Various Surgical Models (PK Populations)



Abbreviations: PK = pharmacokinetic; TKA = total knee arthroplasty
Reproduced from Applicant's Submission, 2.5 Clinical Overview, page 32.

The following table (adapted from Dr. Naraharisetti's review) shows the PK parameters of bupivacaine following single dose HTX-011 (bupivacaine/meloxicam) administered by instillation in the surgical site (Phase 2 studies with full PK sampling):

PK parameters of bupivacaine following single dose HTX-011 (bupivacaine/meloxicam) administered by instillation in surgical procedures (Phase 2 studies with full PK sampling).

Surgical Procedure	Bunionectomy (Study 208)	Herniorrhaphy (Study 202)	Total Knee Arthroplasty (Study 209)	Augmentation Mammoplasty (Study 211)	Complete Abdominoplasty (Study 203)
Dose (Volume)	60 mg/1.8 mg (2.1 mL)	300 mg/9 mg (10.3 mL) plus, fentanyl 50 mcg IV	400 mg/12 mg (13.7 mL)		
N	17	16	53 (without ropivacaine) ^a	49	17 (Part C)
C _{max} (ng/mL)	54 ± 33	271 ± 147	695 ± 411	710 ± 246	366 ± 127
AUC ₀₋₂₄ (h·ng/mL)	883 ± 538	4712 ± 2144	11223 ± 6142	11758 ± 3990	5327 ± 1590
AUC ₀₋₄₈ (h·ng/mL)	1371 ± 910	9740 ± 5021	23580 ± 14035	19042 ± 6692	12090 ± 3939
AUC ₀₋₇₂ (h·ng/mL)	1595 ± 1085	12980 ± 6687	30807 ± 20122 (n=50)	23563 ± 8192	16051 ± 16051
AUC _{0-t} ^b (h·ng/mL)	1681 ± 1154	15174 ± 8545	35890 ± 28400	27363 ± 9227	18040 ± 6943
AUC _{inf} (h·ng/mL)	1718 ± 1211	15524 ± 8921	38173 ± 29400 (n=50)	31072 ± 17998	18247 ± 7069
T _{max}	3 [1.55, 24]	18 [3, 30]	21 [4, 59]	4 [1, 35]	25 [9, 38]
C _{last} (120 h) (ng/mL)	0.18 ± 0.14	10 ± 15	5 ± 20 ^c	35 ± 71	9 ± 8
Half-life (h)	15 ± 8	16 ± 9	17 ± 7 (n=50)	25 ± 20	14 ± 3

PK parameters values are arithmetic mean ± standard deviation, except for T_{max} for which it is median (minimum, maximum)

Notes:

^a In TKA study, HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). PK parameters of only HTX-011 without ropivacaine (N=53) are reported

^b AUC_{0-t} is 0 to 120 h post-dose for all studies, except for Study 209, where it is 240h post dose

^c Conc at 144 h

The figures and table above demonstrate the following (adapted from Dr. Naraharisetti's review):

- Observed bupivacaine C_{max} values for the HTX-011 dose 400 mg/12 mg were variable (695 ng/mL for TKA vs. 710 ng/mL Augmentation Mammoplasty vs. 366 ng/mL for Complete Abdominoplasty). Therefore, the expected systemic exposure of bupivacaine does not correlate with the dose. Based on this, it can be concluded that the systemic absorption of bupivacaine or meloxicam of HTX-011 is dependent upon type of surgical procedure, surgical site and the vascularity of the administration site.
- Observed bupivacaine C_{max} values for the HTX-011 dose of 300 mg/9 mg of 271 ng/mL for Herniorrhaphy is similar to the larger HTX-011 dose of 400 mg/12 mg of 366 ng/mL for the larger incision required for Complete Abdominoplasty.
- The AUC_{inf} calculations between the Herniorrhaphy and Complete Abdominoplasty are also comparable and not consistent with the larger dose administered and the larger incision of the Complete Abdominoplasty.

- For HTX-011 400 mg/12 mg, the Tmax of bupivacaine ranges between 1h and 59h. Therefore, the duration of action of HTX-011 is highly variable at the same dose.

In the HTX-011 clinical trials, in addition to listed drug MARCAINE (NDA 016964), the Applicant also used other IR bupivacaine HCl NDA and ANDA products. The following is reproduced from Dr. Naraharisetti's review.

In response (dated 12/21/2018), Applicant mentioned that they had to use other products due to limited supply and drug shortage of branded product MARCAINE. Applicant also added that the bupivacaine HCl drug products used in HTX-011 clinical trials were assigned a therapeutic equivalence code of "AP" to the reference listed drug MARCAINE per Orange Book (Table 1 [below]).

Table 1: ANDA and NDA numbers of bupivacaine HCl used in Phase 2 and Phase 3 studies.

Clinical Study Phase	Bupivacaine hydrochloride injection, USP Manufacturer	NDC #	NDA# or ANDA#
Phase 3	Hospira Inc.	0409-1162-01 ^a	018053 ^b
	Hospira Inc.	0409-1159-02 ^a	018053 ^b
Phase 2	Hospira Inc.	0409-1159-02	018053 ^b
	Hospira Inc.	0409-1159-19	018053 ^b
	Hospira Inc.	0409-1160-01	018053 ^b
	Hospira Inc.	0409-1160-18	018053 ^b
	Hospira Inc.	0409-1162-19	018053 ^b
	Hospira Inc.	0409-1559-30	016964 ^b (RLD)
	Hospira Inc.	0409-1160-10	Not Located
	Hospira Inc.	0409-1749-29	016964 (RLD) ^{b, c}
	Auromedics (Aurobindo)	55150-0168-30	203895 ^d
	Auromedics (Aurobindo)	55150-0169-10	203895 ^d
	APP, Fresenius Kabi USA, LLC	63323-0465-57	018304 ^d

^a Corresponds to List Numbers 11620486 for Study HTX-011-301 and 1159-04-87 for Study HTX-011-302 presented in SN0006.

^b Listed as an NDA number on the Drugs@FDA Website.

^c NDC number is for bupivacaine hydrochloride with epinephrine.

^d Listed as an ANDA number on the Drugs@FDA Website.

Reproduced from Dr. Naraharisetti's Review.

I agree with Dr. Naraharisetti's conclusion regarding the use of other bupivacaine HCl products:

Since the bupivacaine HCl drug products used were assigned a therapeutic equivalence code of "AP" to reference listed drug MARCAINE per Orange Book, these products are expected to have similar PK, thereby same clinical effect and safety profile as that of MARCAINE. Overall, from a scientific/clinical perspective, the outcome/data from the studies is unlikely to be impacted by different marketed products.

Dr. Naraharisetti's review provides the following summary of findings (reproduced):

- Clinical bridge:
 - Across five PK studies, when the highest observed bupivacaine exposure was compared between HTX-011 400 mg/12 mg and reference drug,

bupivacaine HCl, both C_{max} and AUC values of bupivacaine from HTX-011 are higher compared to bupivacaine HCl. For the herniorrhaphy procedure with HTX-011 300 mg/9 mg dose, the C_{max} is lower for HTX-011, while AUC is higher for HTX-011 compared to bupivacaine HCl.

Therefore, HTX-011 300 mg/9 mg should be approvable.

- When the C_{max} and AUC of meloxicam of HTX-011 is compared to the PK parameters of MOBIC, both C_{max} and AUC of meloxicam from HTX-011 are lower than that of MOBIC.
- Among the three surgical procedures (i.e. augmentation mammoplasty, complete abdominoplasty, total knee arthroplasty) that used the same dose of HTX-011 400 mg/12 mg, the systemic exposure in terms of C_{max} and AUC is different. Systemic absorption of bupivacaine or meloxicam from HTX-011 is dependent upon surgical site, surgical procedure and the vascularity of the administration site.
- Within procedure administration of HTX-011 by instillation exhibits dose-linear PK for both meloxicam and bupivacaine (based on two doses in bunionectomy and herniorrhaphy)
- Instillation of HTX-011 with cone-shaped applicator results in higher exposure (C_{max} and AUC) and lower coefficient of variation for both bupivacaine and meloxicam compared to without cone-shaped applicator.
- Based on QT Interdisciplinary Review Team review, ZYNRELEF, at single doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval.
- Based on Pharmacometrics team review of the population pharmacokinetic analysis, the age, sex, race, and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of bupivacaine and meloxicam in ZYNRELEF
-  (b) (4)

In addition, the following is adapted from Dr. Narahariseti's review.

Bupivacaine HCl administered together with Zynrelef™ may impact the overall systemic exposure of bupivacaine. In addition, the toxic effects of meloxicam are additive. Therefore, meloxicam administered with Zynrelef™ may impact the overall systemic exposure of meloxicam.

I concur with the review team that the information submitted in support of the application is acceptable from the clinical pharmacology perspective for the maximum dose of HTX-011 300 mg/9 mL.

6. Clinical Microbiology

Zynrelef™ is not a therapeutic antimicrobial therefore clinical microbiology data were neither required or submitted.

7. Clinical/Statistical- Efficacy

The Applicant has conducted two Phase 3 clinical studies to support the efficacy of their product, Study HTX-011-301 in subjects undergoing bunionectomy and Study HTX-011-302 in subjects undergoing inguinal herniorrhaphy. The design of the pivotal Phase 3 studies are well described in Dr. Petit-Scott's Clinical Review and in Dr. Ren's and Dr. Zhou's Statistical Review and Evaluation. Their reviews will be briefly discussed.

The following is adapted from the Statistical Review by Drs. Ren and Zhou:

These [two Phase 3 clinical studies, HTX-011-301 and HTX-011-302] were randomized (R), multicenter (MC), double-blind (DB), placebo and active-controlled studies. Subjects with inadequately controlled pain symptoms could request rescue analgesia (oral immediate-release (IR) oxycodone, IV morphine and/or oral acetaminophen).

In both Phase 3 studies, the applicant's primary efficacy endpoint was the mean area under the curve (AUC) of numeric rating scale with activity (NRS-A) pain intensity (PI) scores through 72 hours (AUC₀₋₇₂) for HTX-011 compared with saline placebo. The applicant's key secondary efficacy endpoints were:

1. Mean AUC₀₋₇₂ of the NRS-A PI scores for HTX-011 compared with bupivacaine HCl;
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo;
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl;
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

A strict hierarchical testing procedure was applied to control study-wise alpha level at 0.05. The difference between treatment groups for AUC₀₋₇₂ was assessed by an analysis of variance (ANOVA) model with a factor of treatment. In both Phase 3 studies, the results indicated there was a statistically significant reduction in pain intensity with activity compared to both bupivacaine and saline placebo for up to 72 hours. A statistically significant reduction in total opioid consumption over 72 hours was also observed for HTX-011 compared to both bupivacaine and placebo. The proportion of subjects who were opioid-free through 72 hours was statistically significantly higher for HTX-011 compared to bupivacaine.

Since both Phase 3 studies were conducted in an inpatient setting, subject discontinuation was not an issue. However, there was a high percentage of subjects in each study that used rescue medication. The applicant utilized a windowed worst observation carried forward (wWOCF) method to account for this in the analyses of the primary and the 1st key secondary endpoints. With this method, PI scores observed during the analgesic window (duration of effect) of any opioid rescue medication were replaced with the worst observed pre-window PI score unless the observed scores were higher than the worst observed pre-window PI score. Additional sensitivity analyses were conducted also considering non-opioid rescue medication, ignoring the use of rescue medication (using pain scores observed after taking rescue medication), and an integrately assessing pain scores (after using rescue medication) and total use of rescue medication (Silverman et.al., 1993). These sensitivity analyses all supported the primary efficacy analysis, there was a significant treatment effect noted for HTX-011 when compared to placebo and bupivacaine.

Based on the review of the two Phase 3 studies submitted, there is sufficient evidence that the proposed study drug, HTX-011 (60 mg bupivacaine/1.8 mg meloxicam and 300 mg bupivacaine/9 mg meloxicam) administered as a single dose, is efficacious to reduce pain for up to 72 hours after unilateral bunionectomy and unilateral open herniorrhaphy surgery.

Demographics and baseline characteristics are presented in the tables below for each study (reproduced from HTX-011-301 and HTX-011-302 Study Reports, Applicant's Submission).

HTX-011-301: Summary of Demographic and Baseline Characteristics
(Intent-to-Treat Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	Total (N=412)
Age (years)^a				
Mean (SD)	48.0 (14.47)	47.3 (12.83)	45.5 (14.79)	46.9 (14.22)
Median	50.0	49.0	45.0	48.0
Min, Max	18, 77	19, 77	18, 77	18, 77
Sex, n (%)				
Male	19 (12.1%)	14 (14.0%)	23 (14.8%)	56 (13.6%)
Female	138 (87.9%)	86 (86.0%)	132 (85.2%)	356 (86.4%)
Ethnicity, n (%)				
Hispanic or Latino	47 (29.9%)	32 (32.0%)	49 (31.6%)	128 (31.1%)
Not Hispanic or Latino	110 (70.1%)	68 (68.0%)	106 (68.4%)	284 (68.9%)
Race, n (%)				
American Indian or Alaska Native	1 (0.6%)	0	2 (1.3%)	3 (0.7%)
Asian	8 (5.1%)	2 (2.0%)	1 (0.6%)	11 (2.7%)
Black or African Descent	24 (15.3%)	12 (12.0%)	22 (14.2%)	58 (14.1%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.6%)	1 (0.2%)
White	123 (78.3%)	86 (86.0%)	128 (82.6%)	337 (81.8%)
Multiple	1 (0.6%) ^b	0	1 (0.6%) ^c	2 (0.5%)
BMI (kg/m²)				
Mean (SD)	27.31 (4.793)	27.91 (5.050)	27.15 (4.376)	27.39 (4.704)
Median	26.81	27.27	26.74	26.91
Min, Max	18.3, 38.6	17.5, 38.4	17.3, 38.5	17.3, 38.6

Abbreviations: BMI, body mass index; ITT, Intent-to-Treat.

^a Age was calculated relative to the date of informed consent.

^b Asian and White.

^c Black or African Descent and White.

Sources: [Table 14.1.5.1](#), [Listing 16.2.4.1](#).

Source: HTX-011-301 Study Report, Applicant's Submission, NDA 211988

HTX-011-302: Summary of Demographic and Baseline Characteristics
(Intent-to-Treat Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	Total (N=418)
Age (years)^a				
Mean (SD)	48.9 (13.29)	48.0 (14.59)	49.4 (11.26)	48.9 (12.75)
Median	50.0	50.5	51.0	51.0
Min, Max	22, 83	19, 82	18, 69	18, 83
Sex, n (%)				
Male	152 (92.7%)	79 (96.3%)	164 (95.3%)	395 (94.5%)
Female	12 (7.3%)	3 (3.7%)	8 (4.7%)	23 (5.5%)
Ethnicity, n (%)				
Hispanic or Latino	43 (26.2%)	30 (36.6%)	51 (29.7%)	124 (29.7%)
Not Hispanic or Latino	121 (73.8%)	52 (63.4%)	121 (70.3%)	294 (70.3%)
Race, n (%)				
American Indian or Alaska Native	2 (1.2%)	0	0	2 (0.5%)
Asian	2 (1.2%)	1 (1.2%)	2 (1.2%)	5 (1.2%)
Black or African Descent	17 (10.4%)	3 (3.7%)	16 (9.3%)	36 (8.6%)
Native Hawaiian or Other Pacific Islander	4 (2.4%)	0	1 (0.6%)	5 (1.2%)
White	139 (84.8%)	78 (95.1%)	153 (89.0%)	370 (88.5%)
BMI (kg/m²)				
Mean (SD)	27.14 (4.386)	28.12 (4.232)	26.86 (3.578)	27.21 (4.058)
Median	26.90	27.99	26.44	26.75
Min, Max	17.9, 38.5	17.6, 38.5	19.4, 37.9	17.6, 38.5

Abbreviations: BMI, body mass index; ITT, Intent-to-Treat.

^a Age was calculated relative to the date of informed consent.

Source: Table 14.1.5.1.

Source: HTX-011-302 Study Report, Applicant's Submission, NDA 211988

The Demographic tables above for Study 301 and 302 show reasonable uniformity of the patient population across the treatment groups. The preponderance of males in Study 302 is reasonable given the surgical models was inguinal herniorrhaphy where the incidence of inguinal hernia is more common in men. The preponderance of women in Study 301 is also reasonable give the surgical model of bunionectomy where there is an increase incidence of bunions in women.

The following tables describes the patient disposition information for both studies (reproduced from Dr. Ren's and Zhou's review).

Table 2: Subject Disposition in Study HTX-011-301 – Number (%) of Subjects			
	Saline Placebo	Bupivacaine Hcl 50 mg	HTX-011 60mg/1.8 mg
Randomized	109	165	164
ITT population	100	155	157
Completed the 72-hour period	99 (99%)	154 (99%)	155 (99%)
Completed the study	99 (99%)	152 (98%)	154 (99%)
Reasons for study withdrawal			
AE			1 (1%)
Lost to follow-up	1 (1%)	1 (1%)	1 (1%)
Withdrawal by subject		1 (1%)	1 (1%)
Death		1 (1%)	

Source: Reviewer's analyses.

Source: Statistical Review and Evaluation, Dr. Ren and Dr. Zhou

Table 12: Subject disposition in Study HTX-011-302 – Number (%) of Subjects			
	Saline Placebo	Bupivacaine Hcl 75 mg	HTX-011 300mg/9 mg
Randomized	89	179	178
ITT population	82	172	164
Completed the 72-hour period	81 (99%)	170 (99%)	162 (99%)
Completed the study	81 (99%)	170 (99%)	159 (97%)
Reasons for study withdrawal			
Lost to follow-up			1 (1%)
Withdrawal by subject	1 (1%)	2 (1%)	3 (2%)
Protocol deviation			1 (1%)

Source: Reviewer's analyses.

Source: Statistical Review and Evaluation, Dr. Ren and Dr. Zhou

Overall, the Subject Disposition Tables show that there were very few subjects withdrawn for the studies. Specifically, there was only one protocol deviation and a low percentage of patients lost to follow-up.

The following table summarizes the efficacy endpoints results for the Phase 3 studies.

Results for the Primary and Key Secondary Endpoints in Study HTX-011-301 and HTX-011-302

	Study 301 (Bunionectomy)			Study 302 (Herniorrhaphy)		
	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
AUC₀₋₇₂ of the NRS-A (wWOCF)						
Mean (SD)	445.34 (155.792)	393.45 (153.756)	323.29 (182.641)	350.82 (171.224)	341.88 (158.303)	269.39 (173.719)
<u>Primary endpoint:</u> p-value ^a vs saline placebo			<0.0001			0.0004
<u>1st key secondary endpoint:</u> p-value ^a vs bupivacaine HCl			0.0002			<0.0001
Total Opioid Consumption 0-72 Hours (MME)						
Mean (SD)	30.06 (21.016)	25.09 (21.553)	18.80 (19.801)	17.53 (18.908)	14.51 (18.185)	10.85 (17.062)
Median (Min, Max)	25.00 (0.0, 80.0)	17.50 (0.0, 92.5)	12.50 (0.0, 83.0)	11.25 (0.0, 73.5)	7.25 (0.0, 87.5)	0.00 (0.0, 103.0)
<u>2nd key secondary endpoint:</u> p-value ^b vs saline placebo			<0.0001			0.0001
<u>4th key secondary endpoint:</u> p-value ^b vs bupivacaine HCl			0.0022			0.0240
Opioid-Free 0-72 Hours						
n (%)	2 (2.0%)	17 (11.0%)	45 (28.7%)	18 (22.0%)	69 (40.1%)	84 (51.2%)
<u>Other secondary endpoint:</u> p-value ^c vs saline placebo			<0.0001			<0.0001
<u>3rd key secondary endpoint:</u> p-value ^c vs bupivacaine HCl			0.0001			0.0486

Abbreviations: AUC, area under the curve; ITT, Intent-to-Treat; MME, milligram morphine equivalents; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation.

^a p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

^b p-values were obtained using the Wilcoxon rank sum test.

^c p-values from Fisher's exact test.

Sources: Study 301 CSR, Table 14.2.1.1, Table 14.2.2.1, Table 14.2.3.1 and Study 302 CSR, Table 14.2.1.1, Table 14.2.2.1, Table 14.2.3.1.

Source: Summary of Clinical Efficacy, p.62 (PDF), Applicant's submission, NDA 211988

I agree with Dr. Petit-Scott's following conclusions (adapted):

- In the Phase 3 studies, the results did demonstrate a statistically significant difference in mean AUC of pain intensity scores with activity through 72 hours in patients treated with HTX-011 compared to bupivacaine HCl (key secondary efficacy endpoint).
- HTX-011 demonstrated a significant reduction of post-operative pain (primary endpoint) after bunionectomy and open inguinal herniorrhaphy with mesh, when compared to saline placebo. While bupivacaine alone did not perform as well in the herniorrhaphy setting in Study HTX-011-302 as it did in the setting of bunionectomy, Study HTX-011-301, HTX-011 was consistently better than placebo and bupivacaine alone and the key secondary endpoints all trended in support of the primary endpoint.

In addition, the side-by-side comparison of Study 301 and 302, in the table above, demonstrate that the subjects in Study 301 (bunionectomy) required higher doses of opioids and fewer patients were opioid free than in Study 302. The following table demonstrates that the difference in opioid use cannot be attributed to the use of non-opioid analgesics, since the subjects in Study 301 required more non-opioid rescue pain medications in all treatment groups compared to Study 302.

Summary of Number of Patients Requiring Rescue Medication Use Through 72 Hours-Study 301 and Study 302

	Study 301			Study 302		
	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
Opioid rescue medications						
Oxycodone/oxycodone hydrochloride ^a	98 (98.0%)	138 (89.0%)	112 (71.3%)	62 (75.6%)	100 (58.1%)	76 (46.3%)
Morphine/morphine sulfate ^b	54 (54.0%)	68 (43.9%)	42 (26.8%)	41 (50.0%)	42 (24.4%)	38 (23.2%)
Fentanyl ^c	0	0	0	0	1 (0.6%)	2 (1.2%)
Hydrocodone ^c	0	0	0	0	0	1 (0.6%)
Non-opioid rescue medications						
Paracetamol/acetaminophen	85 (85.0%)	127 (81.9%)	122 (77.7%)	50 (61.0%)	104 (60.5%)	82 (50.0%)

Abbreviation: ITT, Intent-to-Treat.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. Medications are coded to generic drug names using the World Health Organization (WHO) Drug dictionary, Version 01 September 2016. At each level of summarization (any medication, generic drug name), subjects reporting use of more than one medication are counted only once.

^a Subjects taking oxycodone and/or oxycodone hydrochloride were pooled.

^b Subjects taking morphine and/or morphine sulfate were pooled.

^c Protocol deviation.

Sources: Study 301 CSR, Table 14.1.8.2, Post Hoc Table 14.1.8.6 and Study 302 CSR, Table 14.1.8.2, Post Hoc Table 14.1.8.6.

Source: Summary of Clinical Efficacy, p. 71 (PDF), Applicant's submission, NDA 211988.

Additionally, in the table above titled “Results for the Primary and Key Secondary Endpoints in Study HTX-011-301 and HTX-011-302” for the key secondary endpoint of the mean total opioid consumption from 0 to 72 hours the difference between the bupivacaine group, which is the current standard of care, and HTX-011 is 3.66 MMEs. This is a nominal reduction in MMEs, therefore the opioid reduction in Study 302 is not clinically meaningful when comparing bupivacaine and HTX-011.

Moreover, the following table shows that most patients that were opioid-free at 72 hours remained opioid-free at Day 10 and 28 for both studies. However, when comparing Study 301 and 302 it is clear that more patients were opioid free at day 10 and 28 in Study 302 (herniorrhaphy) compared to Study 301 (bunionectomy). This is important because it demonstrates that any reduction in opioid use attributed to the use of local anesthetic is dependent on the clinical model and may not be suitable for extrapolation across clinical settings. In addition, comparing opioid-free patients through Day 10 and 28, there is no statistical significance between the HTX-011 group and the bupivacaine group in Study 302.

Proportion of Subjects Who Were Opioid-Free Through Day 10 or Through Day 28 in Studies HTX-011-301 and HTX-011-301 (ITT Population)

	Study 301			Study 302		
	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
All Subjects						
Opioid-free through Day 10	2 (2.0%)	15 (9.7%)	41 (26.1%)	18 (22.0%)	67 (39.0%)	80 (48.8%)
p-value vs PBO			<0.0001			<0.0001
p-value vs BPV			0.0002			0.0787
Opioid-free through Day 28	2 (2.0%)	14 (9.0%)	37 (23.6%)	17 (20.7%)	60 (34.9%)	71 (43.3%)
p-value vs PBO			<0.0001			0.0007
p-value vs BPV			0.0007			0.1189
Subjects who were opioid-free through 72 hours						
N	2	17	45	18	69	84
Remained opioid-free through Day 10	2/2 (100.0%)	15/17 (88.2%)	41/45 (91.1%)	18/18 (100.0%)	67/69 (97.1%)	80/84 (95.2%)
Remained opioid-free through Day 28	2/2 (100.0%)	14/17 (82.4%)	37/45 (82.2%)	17/18 (94.4%)	60/69 (87.0%)	71/84 (84.5%)

Abbreviations: BPV, bupivacaine HCl; ITT, Intent-to-Treat; PBO, saline placebo.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. Opioid-free through 72 hours was defined as having total morphine milligram equivalent (MME) opioid dose = 0 during the 72-hour postoperative period, based on concomitant medication data. Opioid-free through Day 10 was defined as MME = 0 through 72 hours and answering "No" to the diary question "Did you take any opioid medication?" every day from 72 hours through Day 10. Opioid-free through Day 28 was defined similarly. Subjects who answered "Yes" or had a missing answer on any day during the period, or withdrew from the study during the period, were not considered opioid-free. A total of 64 subjects in Study 301 did not receive a diary upon discharge; concomitant medication data was used for these 64 subjects for opioid-free analyses through Day 10 and Day 28.

P-values from Fisher's exact test.

Sources: Study 301 CSR, Post Hoc Table 14.2.3.5, Post Hoc Table 14.2.3.6 and Study 302 CSR, Post Hoc Table 14.2.3.5, Post Hoc Table 14.2.3.6.

Source: Summary of Clinical Efficacy, p.73 (PDF), Applicant's submission, NDA 211988

Even though the data for Study 302 are not as statistically significantly different as for Study 301 when, compared to bupivacaine HCl, there is a benefit when comparing HTX-011 to placebo (primary endpoint) in both pivotal studies. Therefore, I agree with the Statistical Review and Evaluation by Dr. Ren and Dr. Zhou and the Clinical Review of Dr. Petit-Scott's conclusion that the results of the Phase 3 studies support the approval of HTX-011 60 mg/1.8 mg for bunionectomy and 300 mg/9 mg for inguinal herniorrhaphy for this marketing application.

8. Safety

The following is adapted from Dr. Petit-Scott's review.

The evaluation of the safety profile for HTX-011 involved a comprehensive review of adverse events suspected to be related to the drug products, bupivacaine and meloxicam, and those suspected to be related to the novel Biochronomer® formulation or excipients in the formulation.

There were no issues of data integrity or the overall quality of the submission.

In addition, the following was adapted from Dr. Petit-Scott's review.

A total of 1077 patients were administered a single dose of HTX-011, ranging from 30 mg/0.9 mg to 600 mg/18 mg, in the clinical development program (data from recently submitted Phase 2 studies, 215 and 218, are not included due to incomplete final study reports). With the exception of ten healthy volunteers in Study 102, a Phase 1 study, all patients received HTX-011 during a surgical procedure. The Applicant conducted eight clinical studies using the intended commercial formulation.

However, a total of 448 patients received the intended commercial formulation of HTX-011 via the intended route of administration, currently described as instillation using a unique applicator without a needle, in the two Phase 2b and two Phase 3 studies. However, this safety database is adequate to evaluate HTX-001 in the pivotal studies given the long-standing knowledge of bupivacaine HCl, the disease active ingredient in HTX-011.

The following table provides an overview of the Phase 2b and Phase 3 Studies contributing to the pooled assessment of safety and the table includes the 448 patients that received the intended commercial formulation of HTX-011 via the intended route of administration.

Overview of Phase 3 and Phase 2b Studies Contributing to the Pooled Assessment of Safety HTX-011

Study (Region)	Study Design	Surgery	Treatment Group (Number of Subjects)
301 (US)	Phase 3, randomized, double-blind, placebo- and active-controlled efficacy and safety study	Unilateral simple bunionectomy	- HTX-011 60 mg/1.8 mg via instillation (157) - Bupivacaine HCl 0.5% 50 mg via injection (154) - Saline placebo via instillation (101)
302 (US and Belgium)	Phase 3, randomized, double-blind, placebo- and active-controlled efficacy and safety study	Unilateral open inguinal herniorrhaphy	- HTX-011 300 mg/9 mg via instillation (163) - Bupivacaine HCl 0.25% 75 mg via injection (173) - Saline placebo via instillation (82)
209 (US)	Phase 2b, randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Total knee arthroplasty	- HTX-011 200 mg/6 mg via periarticular instillation (20) - HTX-011 400 mg/12 mg via periarticular instillation and ropivacaine 50 mg via periarticular injection (56) - HTX-011 400 mg/12 mg via periarticular instillation (58) - Bupivacaine HCl 0.25% 125 mg via periarticular injection (65) - Saline placebo via periarticular injection (64)
211 ^a (US) Cohort 4	Phase 2b, randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Bilateral augmentation mammoplasty	HTX-011 400 mg/12 mg (200 mg/6 mg per side) via instillation administered in each of the surgical incision lines (50)

Abbreviations: PK, pharmacokinetics; US, United States.

Note: the number of subjects in each treatment group is based on the Safety Population.

^a Study 211 included additional cohorts to evaluate HTX-011 administered by nerve block. These cohorts are not included in the integrated analysis of safety. Saline placebo and bupivacaine HCl are also not included because they were administered by nerve block. Because only 200 mg/6 mg of HTX-011 was administered into each incision, local safety in this study was assessed at a 200 mg/6 mg dose and systemic safety at a 400 mg/12 mg dose.

Sources: Module 5, Section 5.3.5.1, Study 301 CSR, Study 302 CSR, Study 209 CSR, Study 211 CSR.

Source: Summary of Clinical Safety, p.20 (PDF), Applicant's submission, NDA 211988

This table includes the study of the HTX-011 400 mg/12 mg dose in two Phase 2 studies in different surgical models than the pivotal Phase 3 studies. The applicant proposed the HTX-011 400 mg/12 mL dose for approval. However, the number of patients exposed to the higher dose were inadequate to support the approval of HTX-011 400 mg/12 mg.

Furthermore, Dr. Petit-Scott notes that the safety database is adequate to only support procedure specific indications for the use of HTX-011, reproduced from her review.



Dr. Petit-Scott's outlines the following adverse events of clinical interest in her review (adapted).

The adverse events of most clinical significance with administration of HTX-011 include LAST-related adverse events, cardiovascular thrombotic and gastrointestinal adverse events, and wound-related adverse events, and are loosely categorized by likely causal factor as follows:

- Bupivacaine
 - LAST-related adverse events
- Meloxicam
 - Cardiovascular thrombotic adverse events (Mobic® box warning)
 - Gastrointestinal adverse events (Mobic® boxed warning)
- Biochronomer® formulation or excipients
 - Local inflammatory adverse events (also referred to as wound-related adverse events in this review)
 - Other observed local toxicities, including those observed in nonclinical studies and those included in the Sustol® label

The following summary is adapted from Dr. Petit-Scott's review regarding wound healing.

Considering the totality of the wound healing data and information presented in this NDA submission, there appears to be an increased incidence of wound-related adverse events associated with administration of HTX-011 60 mg/1.8 mg in a bunionectomy wound. The nonclinical data indicates that the increased incidence may be related to excipients in the Biochronomer® formulation (b) (4)

An additional explanation for the increase in wound-related adverse events in patients treated with HTX-011 after particular surgical procedures may be related to the viscous nature of the drug product. HTX-011 may distort or even disrupt the anatomy of otherwise tight, adherent spaces or cavities. The surgical space for bunionectomy is considered small and tight and thus, may be disrupted by the administration of a viscous liquid, resulting in delayed or even impaired healing.

Despite the documented increases in wound-related adverse events observed after bunionectomy surgery, HTX-011 60 mg/1.8 mg is approvable for use in bunionectomy surgery for the following reasons, adapted from Dr. Petit-Scott's review.

- In the table below, the incidence of any abnormal healing of the wound were similar in the three treatment arms. Furthermore, there were findings of delayed healing and wound dehiscence in all three treatment arms. Wound data was collected to day 42 and showed that there was improvement or resolution of the wound related adverse events in all of the treatment arms.

Summary of Wound Healing Results in Study 301, Bunionectomy (Safety Population)

Wound Healing Parameter n/N (%)	Timepoint	Saline Placebo (N = 101)	Bupivacaine HCl 50 mg (N = 154)	HTX-011 60 mg/1.8 mg (N = 157)
Any abnormal wound healing result	Any Timepoint	82 (81.2%)	130 (84.4%)	127 (80.9%)
Bruising	Any Timepoint	62/101 (61.4%)	94/153 (61.4%)	90/155 (58.1%)
	Day 42 Safety Follow-Up Visit	2/100 (2.0%)	5/151 (3.3%)	3/154 (1.9%)
Erythema	Any Timepoint	48/101 (47.5%)	71/153 (46.4%)	82/155 (52.9%)
	Day 42 Safety Follow-Up Visit	10/100 (10.0%)	16/151 (10.6%)	11/154 (7.1%)
Edema	Any Timepoint	76/101 (75.2%)	104/153 (68.0%)	108/155 (69.7%)
	Day 42 Safety Follow-Up Visit	33/100 (33.0%)	39/151 (25.8%)	42/154 (27.3%)
Heat	Any Timepoint	9/101 (8.9%)	8/153 (5.2%)	22/155 (14.2%)
	Day 42 Safety Follow-Up Visit	0/100 (0%)	1/151 (0.7%)	3/154 (1.9%)
Drainage	Any Timepoint	6/101 (5.9%)	5/153 (3.3%)	7/155 (4.5%)
	Day 42 Safety Follow-Up Visit	0/100 (0%)	1/151 (0.7%)	1/154 (0.6%)
Cellulitis	Any Timepoint	4/101 (4.0%)	2/153 (1.3%)	11/155 (7.1%)
	Day 42 Safety Follow-Up Visit ^a	1/100 (1.0%)	0/151 (0%)	1/154 (0.6%)
Delayed Healing	Any Timepoint	3/101 (3.0%)	7/153 (4.6%)	13/155 (8.4%)
	Day 42 Safety Follow-Up Visit ^a	2/100 (2.0%)	3/151 (2.0%)	7/154 (4.5%)
Dehiscence	Any Timepoint	2/101 (2.0%)	2/153 (1.3%)	8/155 (5.2%)
	Day 42 Safety Follow-Up Visit ^a	1/100 (1.0%)	0/151 (0%)	0/154 (0%)

Notes: surgical wound healing was assessed for the following signs and symptoms prespecified by the FDA: bruising, erythema, edema, heat, drainage, cellulitis, delayed healing, and dehiscence. The results are presented in descending order of frequency in the HTX-011 group.

^a After the Day 42 Visit based on an unscheduled follow-up wound healing assessment or a treatment-emergent adverse event (TEAE) reported for the symptom, all symptoms of cellulitis, dehiscence, or delayed healing resolved except 3 symptoms of delayed healing in 3 subjects.

Source: Module 5, Section 5.3.5.1, Study 301 CSR, Table 37.

Source: Summary of Clinical Safety, p.134 (PDF), Applicant's submission, NDA 211988

- It appears that leakage of excess HTX-011 from the bunionectomy wound is a credible explanation for development of local inflammatory changes in the short-term (less than 42 days). This may be mitigated by language in the DOSAGE AND ADMINISTRATION section of the package insert, with instructions to minimize leakage of the drug onto the skin near the surgical site.
- There were no reported cases in Study 301 and 208 performed in bunionectomy, of adverse boney changes such as fracture, loosening or loss of hardware, or osteomyelitis document by post-operative x-rays. This suggests that the observed wound-related changes observed on physical exam were likely superficial and did not result in long-term disability.

- (b) (4)
[REDACTED]
[REDACTED] was engage by Heron to evaluate the clinical trial wound healing data. He noted that all of the other surgical trials performed using HTX-011 demonstrated no suggestion of abnormal or delayed healing. Therefore, he concluded that results from Study 301 were spurious and not reflective of the overall safety of HTX-011 demonstrated across the entire drug development program. (b) (4) appears to have the credentials to support a level of expertise in wound healing. However, we do not have enough information

regarding the methodology used or the parameters he used to reach his conclusions.

- Regarding soft tissue surgical procedures, in Study 302, patients treated with HTX-011 300 mg/9 mg during IHR surgery did not appear to have an increased incidence of wound-related adverse events compared to patients treated with saline placebo or bupivacaine HCl.

The second main safety concern with HTX-011 administration is the risk of LAST. The risks of developing LAST after administration of HTX-011 and monitoring for signs and symptoms of LAST are related to the following:

- The variable PK profile for HTX-011, as demonstrated after administration of HTX-011 400 mg/12 mg in three different surgical models. The C_{max} , AUC, and T_{max} demonstrated wide variability across the three models evaluated. This variability makes post-operative safety monitoring recommendations challenging.
- The pharmacodynamic response does not correlate with the systemic bupivacaine concentrations, also making safety monitoring recommendations challenging.
- Bunionectomy and IHR with mesh are generally performed on an outpatient basis, such that most patients will be in an unmonitored setting during the time of peak systemic exposure and potential toxicity. This further complicates postoperative safety assessments.
- The maximum recommended dose of bupivacaine delivered via HTX-011 is greater than that recommended in the Marcaine™ product label.
-

Dr. Petit-Scott concluded the following regarding LAST adapted from her review.

Despite the concerns surrounding the development of LAST with administration of HTX-011 in doses greater than those recommended in the Marcaine™ product label, the dose of HTX-011 up to 300 mg/9 mg appears safe for the following reasons.

- There did not appear to be an increased incidence in potential LAST-related adverse events in patients treated with HTX-011 300 mg/9 mg compared to patients treated with saline placebo or bupivacaine HCl in Study 302.
- There was only a single patient treated with HTX-011 300 mg/9 mg with a C_{max} value greater than 1000 ng/mL at T_{max} 33 hours. That patient had one potential LAST-related adverse event, syncope, five hours after study drug administration. However, the patient did not experience any recurrence of symptoms when the serum level of bupivacaine exceeded 1000 ng/mL at 24 hours. Therefore, it is appears unlikely that this event was associated with LAST.
- The safety evaluation of HTX-011 400 mg/12 mg, the highest proposed dose although unlikely to be approved, did not demonstrate an increased incidence of LAST-related adverse events after administration when compared to the bupivacaine HCl treatment group.

- Review of the continuous Holter data from Study 209 and Study 211 and the serial ECG data from Study 301 and Study 302 did not reveal any clinically meaningful differences in measured parameters across treatment groups.
- Administration of HTX-011 may offer a degree of safety over other delayed-release bupivacaine formulations based on the proposed route of administration, instillation. Because HTX-011 is applied to the tissues with a needleless syringe, the risk of intravascular administration is low.

The final safety issue Dr. Petit-Scott discussed in her review addresses the need to include the Mobic® boxed warning in the HTX-011 label. She presents the following arguments that the boxed warning may not be necessary adapted from her review.

- HTX-011 is administered as a single instillation and repeated exposure during the same surgical procedure is not indicated, therefore, the risk of developing a cardiovascular thrombotic or gastrointestinal adverse event appears low.
- The systemic exposure to meloxicam after a single dose of HTX-011 is much lower in both magnitude and duration than that reported in the Mobic® label after a 7.5 mg oral dose, the likelihood these adverse events will occur is quite low.

However, all NSAID-containing products must contain the boxed warnings, including topically administered NSAIDs, and it is not clear if there is a level of exposure that would negate the risk and eliminate the need for the boxed warnings in the label. Therefore, the NSAID boxed warnings are required in the HTX-011 label.

I concur with Dr. Petit-Scotts final assessment of the safety profile of Zynrelef™, adapted from her review:

I conclude that HTX-011 is a safe treatment option for surgical patients undergoing bunionectomy and open inguinal hernia repair with mesh in the doses evaluated during the Phase 3 clinical studies, HTX-011 60 mg/1.8 mg and HTX-011 300 mg/9 mg, respectively. Additional indications and HTX-011 doses will need to be supported by clinical data, which will likely include additional clinical studies.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The safety and efficacy of HTX-011 has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. Refer to Section 11. Postmarketing Requirements and Commitments for additional information on the planned pediatric studies.

11. Other Relevant Regulatory Issues

Dr. Petit-Scott's review includes the following information concerning regarding financial disclosures:

The Applicant disclosed that one investigator, (b) (6) participated in financial arrangements requiring disclosure per 21 CFR part 54. Per form FDA 3455, the Applicant provided information to address the concern for bias, including confirmation that (b) (4) was blinded for the (b) (4) studies for which was a clinical investigator.

Routine audits were conducted at two sites by the Division of Clinical Compliance and Evaluation in the Office of Scientific Investigations (OSI). The rationale for selection of the sites included large subject enrollment, high incidence of non-serious AEs, and large treatment effect size (test versus placebo groups).

The following table, reproduced from Dr. Lee's review, summarizes the information on the sites and the outcomes of the inspections:

	Clinical Investigator Site Address	Site, Study, Enrollment	Inspection Dates	Inspection Outcome*
1	Richard A. Pollak, D.P.M. Endeavor Clinical Trials 8042 Wurzbach Road San Antonio, TX	Site 5 Study 301 59 subjects Study 302 33 subjects	3/22 – 3/28, 2019	NAI*
2	Derek D. Muse, M.D. Jean Brown Research 1045 East 3900 South Salt Lake City, UT	Site 24 Study 301 58 subjects Study 302 69 subjects	2/27 – 3/6, 2019	NAI*

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations

VAI = Voluntary Action Indicated, minor deviations from regulations

OAI = Official Action Indicated, major deviations from regulations

* For both inspections, the Establishment Inspection Report (EIR) has not been received from the field office and the results reported in this Clinical Inspection Summary (CIS) are based on preliminary communication with the field investigator. Upon receipt and review of the EIR at OSI, an addendum to this CIS will be forwarded to the review division if new significant findings are discovered; otherwise, OSI's written postinspection correspondence letter to the inspected entity (to be copied to review division) indicates completion of EIR review with confirmation of the findings as reported in this CIS. VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations; Data unreliable

Source: Clinical Inspection Summary by Dr. John Lee, Good Clinical Practice Assessment Branch (GCPAB), Division of Clinical Compliance Evaluation (DCCE), Office of Scientific Investigations (OSI)

Dr. Lee's overall assessment of findings and recommendation were noted as follows:

The clinical sites of Drs. Muse and Pollack were inspected in support of this NDA review. Based on the inspections of these two clinical sites, the studies (HTX-011-301 and HTX-011-302) appear to have been conducted adequately, and the data generated at these sites appear acceptable in support of the respective proposed indication. The preliminary compliance classification of the inspection outcome for both clinical investigator site inspections is No Action Indicated (NAI).

12. Labeling

Consultations were obtained from the following:

- Division of Medication Error Prevention and Analysis (DMEPA).
- Division of Pediatric and Maternal Health (DPMH).

Their recommendations were considered and incorporated into the label.

Because this application is receiving a Complete Response, the final label edits were not communicated to the Applicant during this review cycle. Discussions with the Applicant regarding the text of the label will be conducted during the next review cycle, however, the following information should be included in the label.

INDICATIONS AND USAGE

The applicant's proposal (b) (4) is not supported by their drug development program.

The applicant conducted the pivotal Phase 3 studies in the following surgical procedures: bunionectomy and inguinal herniorrhaphy with mesh. Therefore, the indication should only include the use of Zynrelef™ in bunionectomy and inguinal herniorrhaphy with mesh.

Furthermore, (b) (4) should not be included in the INDICATIONS AND USAGE section of the label because it does not meet the definition according to 21 CFR 201.5(c)(2).

13. Postmarketing Recommendations

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. The proposed pediatric studies evaluating HTX-011 and the proposed deferral requests are as follows:

- (b) (4)

- The Applicant requested a deferral for study completion because HTX-011 was ready for approval for use in adults before pediatric studies were complete in accordance with section 505B(a)(3)(A)(i). Additional time for study completion was requested based on receiving Agency agreement on the revised draft protocol in late December, 2018, and the ongoing drug shortage for the active comparator, bupivacaine HCl. The deferral request appears to alter the timeline by approximately 6 months.
 - Study 1 will be initiated with adolescents $\geq$ (b) (4) to < 17 years of age. (b) (4)

 - Study initiation is projected for May 2019 and final report submission projected for May 2022.
-  (b) (4)
- The Applicant requested a deferral for study initiation and completion in accordance with section 505B(a)(3)(A)(ii), and until additional safety data has been collected from Study 1 and the after completion of the juvenile animal studies. The timeline for protocol submission and study initiation and completion have not changed from the Agreed iPSP.
 - Study initiation is projected for July 2020 and final report submission projected for June 2023.
 -

Deputy Division Director's Comments

I concur with the review team that the lack of adequate data to support the product's quality precludes approval of the application at this time.

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/

MARTHA A VAN CLIEF
04/30/2019 05:36:49 PM

SHARON H HERTZ on behalf of RIGOBERTO A ROCA
04/30/2019 05:37:13 PM