CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211950Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 6, 2021

To: Michael Puglisi
Regulatory Health Project Manager
Division of Regulatory Operations for Specialty Medicine
Office of Regulatory Operations

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: XIPERE™ (triamcinolone acetonide injectable suspension), for suprachoroidal use

NDA: 211950

In response to the Division of Regulatory Operations for Specialty Medicine (DROSM) consult request dated September 22, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for XIPERE (triamcinolone acetonide injectable suspension).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DROSM on September 22, 2021 and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DROSM on September 22, 2021 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 28, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 211950
Product Name and Strength:	Xipere (triamcinolone acetonide) injectable suspension, 40 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Clearside Biomedical, Inc.
FDA Received Date:	April 30, 2021
OSE RCM #:	2018-2741-1
DMEPA 1 Safety Evaluator:	Nasim Roosta, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1. REASON FOR REVIEW

As part of the approval process for Xipere (triamcinolone acetonide) injectable suspension, the Division of Ophthalmology (DO) requested that we review the proposed Xipere prescribing information (PI), commercial and sample container labels and carton labeling, as well as the sealed compartment labeling (lid) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Clearside submitted their original proposed labels, labeling, and human factors validation study report to NDA 211950 on December 19, 2018. At that time, we reviewed the prescribing information (PI), container labels, and carton labeling and identified areas of vulnerability that may lead to medication errors.[a] The original submission did not include the professional sample container label and carton labeling. Additionally, our review of the human factors validation study results identified several use errors that indicate that the proposed product's user interface design has not been optimized for safe and effective use, and the report does not identify mitigation steps to reduce the risk of the use errors.[b] On October 18, 2019, a Complete Response (CR) Letter was issued for NDA 211950 due to chemistry, manufacturing, and controls (CMC) as well as clinical pharmacology deficiencies; no human factors recommendations from DMEPA were conveyed to Clearside at that time by the review division.

On April 30, 2021, Clearside submitted their complete response to the CMC and clinical pharmacology deficiencies included in the CR letter as a Class 2 resubmission.

1.2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

[a] Roosta, N. Label and Labeling Review for Xipere (NDA 211950). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 29. RCM No.: 2018-2741.

[b] Flint, J. Human Factors Study Report Review for Xipere (NDA 211950). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 09. RCM No.: 2019-1142.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

2. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Based on our evaluation of the prescribing information, commercial and sample container labels, carton labeling, and sealed compartment labeling (lid) received as part of the Class 2 resubmission for NDA 211950, as well as evaluation of our previous DMEPA reviews (Appendix B), we determined that the labels, labeling, and product design may be improved to promote the safe use of this product from a medication error perspective. In the course of our review, DMEPA requested a meeting with DO, OPQ/ONDP and OPQ/OPPQ to discuss our concerns with the strength presentation on the proposed container label and carton labeling. We noted that the strength presentation did not appear to be consistent with USP labeling requirements for injectables. DO presented the historical use of triamcinolone acetonide injectable suspension, stating that in Ophthalmology, Triamcinolone Acetonide Injectable Suspension is known for its 40 mg/mL concentration, and that there is a 0.1 mL injection volume limit with a suprachoroidal administration; thus, DO felt the risk of injecting more volume is low since ophthalmologists would be familiar with the dosing for this product. DO also mentioned that the USP Chapter <7> Labeling for standard strength expression for single-dose and multiple-dose injectables mentions alternatives if there is potential for confusion, and that it is readily understandable for Ophthalmologist to withdraw a dose of 0.1 mL of a 40 mg/mL concentration of triamcinolone acetonide. Based on our conversations with DO, the team aligned in this case with moving forward with "40 mg/mL" as the prominent strength presentation on the proposed container label and carton labeling and we will request that the "4 mg/ 0.1 mL" be removed.

Furthermore, we continue to maintain the same concerns we previously identified with regards to the user interface design based on the HF data from the previous review cycle. Because our concerns and recommendations for user interface considerations were not previously conveyed, we have included them again within this review.

We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Clearside Biomedical, Inc.

3. RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
Highlights of Prescribing Information and General Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The "Dosage Form and Strengths" section includes the dose, which is already in the *Dosage and Administration* section of the highlights.	Including the dosage is redundant information for this particular section of the highlights.	Revise the statement, "(b) (4) in the "Dosage Form and Strengths" section of the highlights to the following: "A single-dose vial of 40 mg/mL sterile triamcinolone acetonide suprachoroidal injectable suspension."
2.	The (b) (4) is duplicated within the established name of the product in the highlights and throughout the prescribing information.		Remove "(b) (4)" from the established name of the product so that the established name reads: "triamcinolone acetonide injectable suspension."
Full Prescribing Information- Section 2 Dosage and Administration			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	In Section 2.2, part A under "Preparation for Administration" includes the concentration of the suspension (i.e., 40 mg/mL) without further clarifying that the there should only be administration of a 0.1 mL dose volume.	The vial contains an excess of overfill to allow for administration of 0.1 mL. We are concerned that users may think that the entire vial contents are to be withdrawn and administered. Expressing the dose volume clearly may help to mitigate the risk of dosing errors.	Revise Section 2.2 to include the dose volume in the description of the vial of triamcinolone acetonide suspension. For example: "A. One single-dose glass vial containing 40 mg/mL of sterile triamcinolone acetonide injectable suspension to allow for administration of a 0.1 mL dose volume."
2.	In step 9 under Section 2.2 "Preparation for Administration", the amount of drug to be	It would be helpful for the user to know exactly how much drug they are to withdraw from the vial, in	Consider adding the volume of drug that is to be withdrawn from the vial to step 9.

	withdrawn from the vial is not specified.	an added effort to mitigate the risk for dosing errors.	For example: "Invert the entire assembly so that the vial is directly above the syringe. Slide the white plunger handle all the way back and forth multiple times to fill the entire syringe (0.1 mL) with drug and remove any remaining air (see figures A and B).
3.	The figures used in the *Preparation for Administration* and *Administration* instructions are not labeled (e.g., Figure A, Figure B, etc.) within the step-by-step instructional text.	Labeling the figures used in the preparation and administration instructions will improve clarity and the tie between the written instructions to the illustrated action required to complete each step.	Label each figure (e.g., figure A, figure B) in the *Preparation for Administration* and *Administration* instructions and update the reference to the figures within the written instructions (e.g., '(see figure A)').
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	Section 3, "Dosage Forms and Strengths" does not contain the product strength.	It is necessary to express the product strength clearly in order to mitigate the risk of dosing errors.	Add the product strength of "40 mg/mL" to Section 3. For example: "XIPERE is a single-dose glass vial containing 40 mg/mL of sterile triamcinolone acetonide injectable suspension administered with the SCS Microinjector®."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16, the overfill volume of suspension contained in the vial is not specified.	It is necessary to express an overfill statement to alert users that not all contents are to be administered and in order to mitigate the risk of dosing errors.	Ensure a statement is included in Section 16 to alert users of overfill volume contained in the vial. This statement should be what is displayed on the container label and carton labeling. For example: "One single-dose glass vial containing overfill to allow for administration of a 0.1 mL

			dose of 40 mg/mL triamcinolone acetonide injectable suspension .”
2.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges outlined in Section 16.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example: “15°C to 25°C (59°F to 77°F)”.
3.	The storage statement, “The drug vial should be protected from light by storing in the carton,” is presented in passive voice and uses the word “should.”	Proper storage of the drug product will help to mitigate the risk of administering deteriorated drug product. Presenting the storage information in passive voice and use of the word “should” may lead to misinterpretation of the intended action as optional as opposed to an action that must happen to promote proper storage of the drug product.	We recommend revising the storage statement, “The drug vial should be protected from light by storing in the carton,” to read “Store drug vial in carton to protect from light.”

4. RECOMMENDATIONS FOR CLEARSIDE BIOMEDICAL, INC.

Table 3. Identified Issues and Recommendations for Clearside Biomedical, Inc. (entire table to be conveyed to Applicant)			
General Issues (Container Labels and Carton Labeling)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The arch graphic over the proprietary name, Xipere, is distracting from the readability of the name. (b) (4)	To avoid medication errors (including product selection errors), the proprietary name should be clearly and prominently displayed without any intervening	Remove the graphic over the proprietary name, Xipere, in accordance with 21 CFR 201.10(a).

	[redacted] (b) (4)	written, printed, or graphic matter.[c]	
2.	Expressing the product's strength as both 4 mg/0.1 mL and 40 mg/mL can cause confusion. Additionally, the vial contains significant overfill but there is no indication of this.	Clearly expressing the product's strength is necessary to mitigate the risk of medication and dosing errors. Stating the product contains overfill will indicate to the user that not all contents within the vial are to be administered.	Remove the "4 mg/0.1 mL" strength from the commercial and sample container labels and carton labeling and instead include the following statement in its place: "*Contains overfill to allow for administration of 0.1 mL dose volume". Additionally, remove "0.9 mL" from the commercial and sample container labels and carton labeling, and replace with net quantity of "0.1 mL*" to indicate that user should note the asterisk for overfill information.
Container Label (vial), Carton Labeling, Packaging label (lid)			
1.	The [redacted] (b) (4) is duplicated within the established name of the product on the sample and trade container labels, sample and trade carton labeling and the packaging label.		Remove "[redacted] (b) (4)" from the established name of the product so that the established name reads: "triamcinolone acetonide injectable suspension"
Container Labels (vial)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The location for the expiration date for the trade container label is not specified. Additionally, the expiration date on the	If the expiration date is not clearly expressed, users can be confused and use an expired product (administration errors).[d]	We recommend that the expiration dates on both the trade and sample container labels appear in the same format as the expiration date format expressed on the packaging label (lid) or

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[d] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

	sample vial label does not specify the date format to be displayed.		carton labeling (i.e., YYYY-MM-DD or MM/YYYY).
2.	The container label (vial) for the trade and sample products do not express the product NDC.	The product's NDC should be clearly expressed in order to prevent product identification/selection errors in the event the vial gets separated from the carton.	We recommend adding an NDC to the container labels for both the trade and sample products. The NDC for the drug product should be unique and different from the NDC for the kit.
Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The carton labeling does not contain a linear barcode.	The linear barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to the carton labeling as required per 21 CFR 201.25(c)(2). The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly.
2.	Both the commercial and sample carton labeling do not include the Fahrenheit temperature range for storage.	All of the temperature ranges for which the product can be stored should be clearly displayed on the carton labeling to prevent the risk of administration of deteriorated drug product.	Add the Fahrenheit temperature range to the storage information on both the trade and sample carton labeling. For example: "15°C to 25°C (59°F to 77°F)"
Sealed Compartment Labeling (lid)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The word "sterile" is not included in the description of the contents within the sealed compartment.	Due to the (b) (4) conditions in which the product is prepared, it is important for the preparer to be aware that sealed compartment contents are sterile as well.	Revise the sealed compartment content statement to include the word "sterile". For example: "Sealed compartment contains the following sterile components:"
Human Factors Validation Study Report Results			

Our previous review of the usability study results identified several missing key elements from the human factors (HF) validation study report that impacted our ability to provide a full review. See our bulleted list below.

Notwithstanding the missing key elements, we reviewed the available data. We note that there were several use errors identified that indicate that the product design has not been optimized for safe and effective use, however, the report does not identify mitigation steps to reduce the occurrence of the use errors and additional data to demonstrate the effectiveness of the mitigations. For example, there were use errors with removing the sterile inner tray, and with attaching and disconnecting the syringe and vial adapter, which may compromise the product's sterility. Additionally, several users did not fill the syringe with enough medication because the 0.1 mL mark on the syringe was not prominent. This use error would result in an underdose. We recommend that you implement additional strategies to optimize the user interface based on these results.

Once you finalize your product user interface, we recommend that you conduct an HF validation study. We expect that your HF validation study report should incorporate the following missing elements to enable a comprehensive Agency's review:

1. An analysis of hazards and risks associated with use of the product in a use-related risk analysis (URRA) evaluating all tasks the user needs to perform. Without this information, we are unable to evaluate the risks associated with all the tasks the user needs to perform.
2. A summary of known use problems with previous models or similar products. Without this information, we are unable to determine whether known problems from similar products may apply to your proposed product.
3. A summary of preliminary analyses and evaluations, including formative evaluations; a discussion of key findings; and any changes made to the user interface (e.g., design change, labeling changes), as well as a discussion of how you used the formative evaluation results and findings to update the product user interface and use-related risk analysis. Without this information, it is unclear how design of the current user interface was informed by formative human factors studies.
4. A detailed description of the test environment and conditions of use. Without this information, we are unable to determine whether the usability study was conducted in an environment that closely simulates the expected use environment.
5. A detailed description of the training provided to participants and rationale for how it corresponds to the training users are expected to receive consistently with the marketed product. Without this information, we are unable to determine whether the training provided to the participants in the usability study was representative of the training they would receive under expected use of the product (if training is applicable).

6. A detailed description of the user tasks selection and categorization (e.g. critical). While there were tasks identified as critical, there was no rationale provided to support your task selection and categorization.
7. The definition of successful performance or failure of each test task at the individual task level. Without this information, we are unable to determine whether we agree with your definitions of performance success or failure.
8. Root cause analysis of all use errors, difficulties, close calls. Root causes should focus on specific aspects of the user interface that the participant is interacting with and whether that might have caused or contributed to the use-related issue. The root cause analysis should be based on the analysis of subjective feedback from your study participants and your analysis.
9. Mitigation steps taken to reduce the occurrence of all use errors, difficulties, close calls. Please note that when you conduct the study and if you observe use related errors and failures, the Agency expects that you apply the human factors engineering process to implement necessary changes to the product user interface. Depending on the nature of changes and the risk, you may need to perform additional human factors validation study to demonstrate the effectiveness of the changes.
10. The moderator script. Without this information, we are unable to determine whether the moderator script contains any leading statements that may bias the study results.

Additionally, we recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Please refer to our draft guidance titled *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*[e] for the content of a human factors validation study protocol and report submission.

[e] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Guidance on human factors procedures to follow can be found in the following guidance documents[f]:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[f]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

[f] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

5. APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Xipere that Clearside Biomedical, Inc. submitted on April 30, 2021.

Table 4. Relevant Product Information for Xipere (triamcinolone acetonide)	
Initial Approval Date	N/A
Active Ingredient	Triamcinolone acetonide
Indication	For the treatment of macular edema associated with uveitis.
Route of Administration	Suprachoroidal
Dosage Form	Injectable suspension
Strength	36 mg/0.9 mL with concentration of 40mg/mL per vial
Dose and Frequency	4 mg (0.1 mL of 36 mg/0.9 mL) injected suprachoroidally once
How Supplied	Each **XIPERE** carton contains a single-dosing tray with: 1. One single-dose glass vial of triamcinolone acetonide suprachoroidal injectable suspension 40 mg/mL 2. Sterile components for administration, sealed in a Tyvek-covered tray: • One SCS Microinjector® syringe with vial adapter attached • One 30-G x 900-µm needle • One 30-G x 1100-µm needle
Storage	Store at 15° to 25°C (59° to 77°F); do not freeze. The drug vial should be protected from light by storing in the carton.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 12, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, "Xipere" and "NDA 211950". Our search identified two (2) previous reviews[g,h] and we considered our previous recommendations to see if they are applicable for this current review. We note that a Complete Response letter was issued to NDA 211950 on October 18, 2019 during the original review cycle for the application. At that time, no label, labeling or human factors recommendations were communicated to the Applicant. With this resubmission, we note that no changes to the user interface (device and labeling) were included in the submission that would alter our previous findings for the labels, labeling and human factors validation results. Thus, we determined that our previously identified concerns have not been addressed. Thus, we include our recommendations pertaining to the labels, labeling, and human factors validation study results as part of our overall assessment of materials reviewed for NDA 211950 in Sections 4 and 5 of this review.

[g] Roosta, N. Label and Labeling Review for Xipere (NDA 211950). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 29. RCM No.: 2018-2741.

[h] Flint, J. Human Factors Study Report Review for Xipere (NDA 211950). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 09. RCM No.: 2019-1142.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Xipere labels and labeling submitted by Clearside Biomedical, Inc.

- Container labels received on April 30, 2021
- Carton labeling received on April 30, 2021
- Professional Sample vial label received on April 30, 2021
- Professional Sample Carton Labeling received on April 30, 2021
- Prescribing Information received on April 30, 2021, available from: \\CDSESUB1\evsprod\nda211950\0017\m1\us\114-label\1141-draft-label\proposed.docx

F.2 Label and Labeling Images

Container label (trade)

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 09, 2019
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 211950
Drug Constituent Name and Strength	Xipere (triamcinolone acetonide suprachoroidal injectable suspension) 40 mg/mL
Device Constituent:	SCS Microinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Clearside Biomedical
Submission Date:	December 19, 2019
OSE RCM #:	2019-1142
DMEPA Human Factors Evaluator:	Jason Flint, MBA, PMP
DMEPA Team Leader (Acting):	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director	Irene Z. Chan, PharmD, BCPS

1. REASON FOR REVIEW

We conducted a review of a human factors (HF) validation study report[1] submitted under NDA 211950 for Xipere (triamcinolone acetonide suprachoroidal injectable suspension). Xipere is a drug administered via a proposed SCS Microinjector syringe that is intended to treat macular edema associated with uveitis.

1.1 PRODUCT DESCRIPTION

The components for administration include one single-dose glass vial of triamcinolone acetonide suprachoroidal injection suspension (40 mg/mL), one SCS Microinjector syringe with vial adapter, one 30-G x 900 micrometer needle, and one 30-G x 1100 micrometer needle (Figure 1). The components are packaged in a sealed outer tray designed to assist the user in placing an internal sterile tray containing the SCS Microinjector and needles onto the preparation surface.

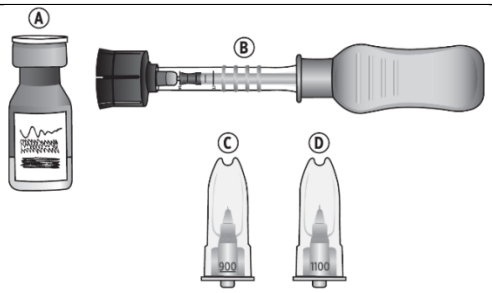

Figure 1: Vial (A), SCS Microinjector with vial adapter (B), and 30 G needles (C,D)

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

Clearside Biomedical did not submit the HF validation study protocol for our review prior to conducting the study and submitting the HF validation study results. Additionally, DMEPA had no prior interactions with Clearside Biomedical and did not provide comments or guidance prior to the NDA submission.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

[1] While we refer to the study as "Human Factors Validation Study" in our review, the study did not demonstrate that the user interface supports safe and effective use of the product by intended users.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E-N/A
Labels and Labeling	F-N/A

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the HF validation study design and our evaluation findings.

3.1 SUMMARY OF STUDY DESIGN

Clearside Biomedical submitted a "SCS Microinjector Usability Study" to "validate that the product packaging, and user/administration instructions support the correct preparation and assembly of the SCS Microinjector, to prime the microinjector with drug and ready it for an injection." The study included 20 retinal and uveitis specialists, who were asked to review the administration instructions "as if they were doing so in the office for the first time." Participants were then asked to demonstrate the assembly of the SCS Microinjector, and were asked follow-up questions to gauge their understanding.

3.2 ASSESSMENT OF STUDY METHODOLOGY

As noted above, the Applicant did not submit the HF validation study protocol for our review prior to conducting the study and submitting the HF validation study results. During our review, we noted the HF validation study report was missing key elements, which raises concerns regarding the utility of the collected data in demonstrating that the user interface supports the safe and effective use of the product. Section 5 details the HF validation report deficiencies and offers recommendations for the Applicant.

3.3 RESULTS AND ANALYSES

Due to the key elements missing from the HF validation study report, a full analysis could not be completed by DMEPA. Additionally, the data we could evaluate are insufficient to support a determination that the user interface supports the safe and effective use of the product by intended users for intended uses and environments. However, despite key elements missing from the HF validation study report, we note that there were several use errors identified that indicate that the product design has not been optimized for safe and effective use, and the report does not identify mitigation steps to reduce the risk of the use errors. For example, there were use errors with removing the sterile inner tray, and with attaching and disconnecting the syringe and vial adapter, which may compromise the product's sterility. Additionally, several users did not fill the syringe with enough medication because the 0.1 mL mark on the syringe was not prominent. This use error would result in an underdose.

We discussed the above results and HF validation study report deficiencies with the Division of Transplant and Ophthalmology Products on September 4, 2019, and learned that there were other issues identified with the application that will preclude approval. Thus, we did not pursue obtaining the missing information from the Applicant during this review cycle.

4. CONCLUSION AND RECOMMENDATIONS

Our review of the usability study results identified several missing key elements from the human factors (HF) validation study report that impacted our ability to provide a full review. Notwithstanding the missing key elements, we reviewed the available data. We note that there were several use errors identified that indicate that the product design has not been optimized for safe and effective use. We recommend the sponsor to implement additional strategies to optimize the user interface, finalize the product user interface, and conduct another HF validation study. We provide letter-ready comments in Section 5 below that can be sent to the Applicant.

5. RECOMMENDATIONS FOR CLEARSIDE BIOMEDICAL

Our review of the usability study results identified several missing key elements from the human factors (HF) validation study report that impacted our ability to provide a full review. See our bulleted list below.

Notwithstanding the missing key elements, we reviewed the available data. We note that there were several use errors identified that indicate that the product design has not been optimized for safe and effective use, however, the report does not identify mitigation steps to reduce the occurrence of the use errors and additional data to demonstrate the effectiveness of the mitigations. For example, there were use errors with removing the sterile inner tray, and with attaching and disconnecting the syringe and vial adapter, which may compromise the product's sterility. Additionally, several users did not fill the syringe with enough medication because the 0.1 mL mark on the syringe was not prominent. This

use error would result in an underdose. We recommend that you implement additional strategies to optimize the user interface based on these results.

Once you finalize your product user interface, we recommend that you conduct another HF validation study. We expect that your HF validation study report should incorporate the following missing elements to enable a comprehensive Agency's review:

1. An analysis of hazards and risks associated with use of the product in a use-related risk analysis (URRA) evaluating all tasks the user needs to perform. Without this information, we are unable to evaluate the risks associated with all the tasks the user needs to perform.
2. A summary of known use problems with previous models or similar products. Without this information, we are unable to determine whether known problems from similar products may apply to your proposed product.
3. A summary of preliminary analyses and evaluations, including formative evaluations; a discussion of key findings; and any changes made to the user interface (e.g., design change, labeling changes), as well as a discussion of how you used the formative evaluation results and findings to update the product user interface and use-related risk analysis. Without this information, it is unclear how design of the current user interface was informed by formative human factors studies.
4. A detailed description of the test environment and conditions of use. Without this information, we are unable to determine whether the usability study was conducted in an environment that closely simulates the expected use environment.
5. A detailed description of the training provided to participants and rationale for how it corresponds to the training users are expected to receive consistently with the marketed product. Without this information, we are unable to determine whether the training provided to the participants in the usability study was representative of the training they would receive under expected use of the product (if training is applicable).
6. A detailed description of the user tasks selection and categorization (e.g. critical). While there were tasks identified as critical, there was no rationale provided to support your task selection and categorization.
7. The definition of successful performance or failure of each test task at the individual task level. Without this information, we are unable to determine whether we agree with your definitions of performance success or failure.
8. Root cause analysis of all use errors, difficulties, close calls. Root causes should focus on specific aspects of the user interface that the participant is interacting with and whether that might have caused or contributed to the use-related issue. The root cause analysis should be based on the analysis of subjective feedback from your study participants and your analysis.

9. Mitigation steps taken to reduce the occurrence of all use errors, difficulties, close calls. Please note that when you conduct the study and if you observe use related errors and failures, the Agency expects that you apply the human factors engineering process to implement necessary changes to the product user interface. Depending on the nature of changes and the risk, you may need to perform additional human factors validation study to demonstrate the effectiveness of the changes.
10. The moderator script. Without this information, we are unable to determine whether the moderator script contains any leading statements that may bias the study results.

Additionally, we recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Please refer to our draft guidance titled *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*[2] for the content of a human factors validation study protocol and report submission.

Guidance on human factors procedures to follow can be found in the following guidance documents[3]:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[3]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/RegulatoryInformation/Guidances/default htm

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www fda.gov/RegulatoryInformation/Guidances/default.htm.

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Xipere (triamcinolone acetonide suprachoroidal injectable suspension) that Clearside Biomedical submitted on December 19, 2019.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Ophthalmic corticosteroid
Active Ingredient (Drug or Biologic)	triamcinolone acetonide
Indication	treatment of macular edema associated with uveitis
Route of Administration	Suprachoroidal injection
Dosage Form	Injectable Suspension
Strength	40 mg/mL
Dose and Frequency	4 mg (0.1 mL of 40 mg/mL) injected suprachoroidally once
How Supplied	The components for administration include: • One single-dose glass vial of triamcinolone acetonide suprachoroidal injectable suspension 40 mg/mL • One SCS Microinjector® syringe with vial adapter attached • One 30-G x 900-µm needle • One 30-G x 1100-µm needle
Storage	Store at 15° to 25°C (59° to 77°F); do not freeze. The drug vial should be protected from light by storing in the carton.
Container Closure	single dose glass vial
Intended Users	Physicians
Intended Use Environment	Health-Care settings

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On September 6, 2019, we searched the L:drive and AIMS using the terms, "Xipere", "211950" and "115683" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[4] relevant to our current review, and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

Clearside Biomedical did not previously submit their HF validation study protocol for our review. As noted above, the SCS Microinjector Usability Study, submitted on December 19, 2019 did not provide information about Clearside Biomedical's human factors engineering process.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\cdsesub1\evsprod\nda211950\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uveitis\5354-other-stud-rep\srus\srus.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX F. LABELS AND LABELING

N/A

[4] Roosta, N. Label and Labeling Review for Xipere (traimcinolone acetonide) injection NDA 211950. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019MAR09. RCM No.: 2018-2741.

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Clinical Inspection Summary

Date	August 20, 2019
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Wiley Chambers, M.D., Deputy Director Jennifer Harris, M.D., Medical Officer Michael Puglisi, Regulatory Project Manager Division of Transplantation and Ophthalmic Products (DTOP)
BLA#	211950
Applicant	Clearside Biomedical, Inc.
Drug	Xipere (triamcinoline acetonide suprachoroidal injectable suspension)
NME	No
Review Priority	Standard
Proposed Indication	Treatment of macular edema associated with uveitis
Consultation Request Date	February 4, 2019
Summary Goal Date	August 26, 2019
Action Goal Date	September 19, 2019
PDUFA Date	October 15, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Rifkin and Wang were inspected in support of this NDA with regard to their conduct of Protocol CLS1001-301. Based on the results of these inspections, the study appears to have been conducted adequately at Dr. Wang's site. The data generated at this site appear acceptable in support of the respective indication. The inspection at Dr. Rifkin's site revealed that three subjects were randomized to the study despite failing to meet eligibility criteria. The review division should consider excluding Subjects (b) (6) (b) (6) and (b) (6) from Dr. Rifkin's site from the per-protocol population analyses.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Xipere (triamcinoline acetonide suprachoroidal injectable suspension) for the treatment of macular edema associated with uveitis.

Clinical inspections were requested for the following protocol in support of this application:

Protocol CLS1001-301,"PEACHTREE: A **P**hase 3, Randomiz**E**d, M**A**sked, **C**ontrolled Clinical Trial to Study the Safety and Efficacy of Triamcinolone Acetonide Injectable Suspension (CLS-TA) for t**H**e **TR**eatment of Subjects with Macular **E**dema associated with Non-Infectious Uv**E**itis Xipere (CLS-TA, triamcinoline acetonide injectable suspension) is a steroid being investigated for the treatment of macular edema associated with uveitis."

The primary objective of the study was to demonstrate the efficacy of CLS-TA in subjects with macular edema associated with non-infectious uveitis as shown by the change from Baseline in Best Corrected Visual Acuity (BCVA) measured using Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

This Phase 3, randomized, masked, sham-controlled, multicenter study included eight visits over a maximum of 27 weeks. Subject eligibility was determined at Visit 1, and qualifying subjects were randomized at Visit 2. Subjects then received two injections of the test article or two sham injections in the study eye twelve weeks apart (Visits 2 and 5). Follow up visits occurred every four weeks, with a final evaluation at 24 weeks (Visit 8) after initial randomization.

The *primary efficacy endpoint* of the study was the proportion of subjects with a change from Baseline of ≥15 ETDRS letters at Visit 8 (24 weeks), subsequent to suprachoroidal injections of CLS-TA or sham SC injection procedures.

Rationale for Site Selection

The sites to be inspected were selected by and identified in the inspection consult issued by the DTOP. Dr. Rifkin's site was selected for inspection because of its relatively high enrollment. Dr. Wang's site was selected for inspection because of its high total risk score.

III. RESULTS:

1. **Site # 102**
   Robert Wang, M.D.
   Texas Retina Associates
   9600 N. Central Expressway, Suite 100
   Dallas, TX
   Inspection Dates: 8-10 Apr 2019

At this study site, 13 subjects were screened, five subjects met rescue criteria, and eight subjects completed the study. The informed consent forms for all 13 enrolled subjects were reviewed, with consent being obtained appropriately prior to any study-related activities.

Source documents for all eight enrolled subjects were audited. Records reviewed included subject eligibility, randomization, intraocular pressures, vital signs, laboratory results, discontinuations, concomitant medications, protocol deviations, IRB, sponsor, and monitor correspondence and study approvals, financial disclosure forms, training documentation, delegation logs, source records, study eligibility, and drug accountability.

The primary efficacy endpoint was verifiable for all eight enrolled subjects, and there appeared to be no under-reporting of adverse events. Source worksheets documenting the number of ETDRS letters read matched the data listings for the eight enrolled subjects other than two instances where discrepant BCVA data entries were attributed to typographical errors that did not affect rescue criteria or the efficacy endpoint.

2. Site #10699
Lana Rifkin, M.D.
Ophthalmic Consultants of Boston
50 Staniford St
Boston, MA
Inspection Dates: 7-12 Mar 2019

At this study site, eight subjects were screened, and four subjects were randomized to the study and completed the study. Subject (b) (6) received rescue medication (Ozurdex implant) after refusing treatment with the second dose of the study drug. The use of the implant was reported in the "Medications" data listing, and a protocol deviation was also reported. The informed consent forms for all eight screened subjects were reviewed with consent being obtained appropriately prior to any study-related activities.

Source documents for the four enrolled subjects were audited. Records reviewed included IRB documentation, financial disclosure, source records, monitoring reports, inclusion/exclusion criteria, masking, randomization, drug dosing, primary efficacy endpoint, concomitant medications, protocol deviations, drug accountability, adverse events, and drug accountability.

The primary efficacy endpoint was verifiable for all four enrolled subjects, and there appeared to be no under-reporting of adverse events. Source worksheets documenting the number of ETDRS letters read matched the data listings for all four enrolled subjects.

A Form FDA 483 was issued noting that Subjects (b) (6) (b) (6) and (b) (6) failed to meet eligibility criteria. Specifically,

- Subjects (b) (6) and (b) (6) who were both randomized to the study drug were erroneously included in the study based on Snellen equivalent numbers read rather than the number of ETDRS BCVA letters read. Even after the ETDRS BCVA values were determined for Subjects (b) (6) and (b) (6) who read 71 and 73 letters, respectively, at Visit 2, the subjects remained in the study and received study drug despite both subjects having failed inclusion criterion #3, which required that subjects be able to read ≤ 70 letters. These study inclusion errors for both subjects were reported as protocol violations.

- Subject (b) (6) who was randomized to the study drug used Durezol QID OU, a corticosteroid, between screening, at visit 2, and throughout the study. This subject was randomized to the study and received study drug despite meeting exclusion criterion #10, which excluded subjects using any ocular corticosteroid in the 10 days prior to Visit 2. This use of a prohibited concomitant medication was reported as a protocol violation.

Dr. Rifkin responded in writing in a letter dated March 25, 2019, acknowledging that three of the four subjects randomized at this site failed inclusion/exclusion criteria. Dr. Rifkin's corrective actions included retraining on the significance of adherence to inclusion/exclusion criteria, the development of listings of prohibited concomitant medications for easy reference, and the use of inclusion/exclusion protocol-specific templates for subject screening.

Reviewer comments: Three of the four subjects enrolled at this site (75%) failed to meet eligibility criteria: two subjects failed to meet protocol-specified visual acuity criteria while a third was treated for the duration of the study with a prohibited concomitant medication. All of the above subjects were randomized to the study drug. The described protocol violations were reported in the CSR. The review division should consider excluding Subjects (b) (6) (b) (6) *and* (b) (6) *from Site #10699 from the per-protocol population analyses.*

{See appended electronic signature page}

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DTOP\Reviewer\Jennifer Harris
DTOP\Project Manager\Michael Puglisi
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OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
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OSI\DCCE\GCPAB\Reviewer\Roy Blay
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 29, 2019
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	NDA 211950
Product Name and Strength:	Xipere (triamcinolone acetonide) injectable suspension, 40mg/mL
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Clearside Biomedical, Inc.
FDA Received Date:	December 19, 2018
OSE RCM #:	2018-2741
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for Xipere (triamcinolone acetonide) injectable suspension 40mg/mL, the Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

During our review of the proposed proprietary name for this product, we noted that it would be available as a single dose vial that would be filled with 0.9 mL (36 mg) to make a concentration of 40 mg/mL. Clearside clarified the dosage strength to be 4 mg in 0.1 mL which is withdrawn from a vial containing 0.9 mL of 40 mg/mL. Upon submission of the NDA, we discussed the strength statement with the Office of Pharmaceutical Quality (OPQ). They stated this strength statement is consistent with other injectable ophthalmic triamcinolone products currently on the market. In addition, we reviewed currently approved injectable ophthalmic products and found two (2) products that are labeled with the strength per single milliliter (i.e., concentration per mL) despite the vial containing less than 1 mL. These products include Lucentis (ranibizumab) and Jetrea (ocriplasmin). Therefore, we find this strength presentation acceptable, but determined the strength presentation and net quantity statements could be further clarified (see Tables 2 and 3).

Tables 2 and 3 below include the identified medication error issues with the submitted packaging, label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Transplant and Ophthalmology (DTOP)

Prescribing Information			
Highlights of Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The "Dosage Form and Strengths" section includes the dose, which is also included in the "Dosage and Administration" section of the highlights. In addition, the volume of solution contained in the vial is not specified.	It is necessary to express the product strength and the volume of the contents in the vial clearly in order to prevent dosing errors.	Revise the statement, "(b) (4) in the "Dosage Form and Strengths" section of the highlights by removing (b) (4) For example: "Single-dose vial containing 0.9 mL of 40 mg/mL sterile triamcinolone acetonide suprachoroidal injectable suspension."
Full Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	In Section 2.2, part A, "Preparation for Administration", the volume of solution (net quantity) is not specified and may mislead users into thinking the entire vial contents are to be withdrawn and administered.	It is necessary to express the volume of the contents in the vial clearly in order to prevent dosing/medication errors.	Revise Section 2.2 to include the volume of solution within the vial. For example: "A. One single-dose glass vial containing 0.9 mL triamcinolone acetonide suprachoroidal injectable suspension 40 mg/mL."
2.	Section 3, "Dosage Forms and Strengths" does not contain the product strength.	It is necessary to express the product strength and the volume of the contents in the vial clearly in order to prevent dosing errors.	Add the product strength of "40 mg/mL" to Section 3. For example: "Single-dose glass vial containing 0.9 mL of 40 mg/mL sterile triamcinolone acetonide suprachoroidal injectable suspension

			administered with the SCS Microinjector®."
3.	Section 16, the volume of solution (net quantity) contained in the vial is not specified.	It is necessary to express the volume of the contents in the vial clearly in order to prevent dosing/medication errors.	Ensure the net quantity statement appears in Section 16 of the PI in accordance with to minimize the risk of overdose where the user could withdraw and administer more than specified dose. For example: "One single-dose glass vial containing 0.9 mL of triamcinolone acetonide suprachoroidal injectable suspension 40 mg/mL"
4.	Figures are not referenced within the instructional text.	To supplement and to illustrate the action required, references to figures should immediately follow the written instruction that the figure illustrates.	Label each figure (e.g. figure A, figure B) in the IFU and refer to the figures within the written instructions (e.g. '(see figure A)').

Table 3: Identified Issues and Recommendations for Clearside Biomedical, Inc. (entire table to be conveyed to Applicant)

General Issues (Container Labels and Carton Labeling)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The graphic over the proprietary name, Xipere, is distracting from the prominence and readability of the name. Also, the graphic (b) (4)	To avoid medication errors (including product selection errors), the proprietary name should be clearly and prominently displayed without any intervening	Remove the graphic over the proprietary name, Xipere, in accordance with 21 CFR 201.10(a).

	(b) (4)	written, printed, or graphic matter.[a]	
Container Labels (vial)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	Expiration date on the vial label does not specify the date format to be displayed.	If the expiration date is not clearly expressed, users can be confused and use an expired product (administration errors).[b]	We recommend that the expiration date on the vial appear in the same format as the expiration date format expressed on the carton labeling (i.e., YYYY-MM-DD).
2.	The container label (vial) does not express the product NDC.	The product's NDC should be clearly expressed in order to prevent product identification/selection errors in the event the vial gets separated from the carton.	Add a NDC to the container label. The NDC for the drug product should be unique and different from the NDC for the kit.
Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The carton labeling does not contain a linear barcode.	The linear barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to the carton labeling as required per 21 CFR 201.25(c)(2). The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly.
Sealed Compartment (lid) Labeling			

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The word “sterile” is not included in the description of the contents within the sealed compartment.	Due to the (b) (4) conditions in which the product is prepared, it is important for the preparer to be aware that sealed compartment contents are sterile as well.	Revise the sealed compartment content statement to include the word “sterile”. For example: “Sealed compartment contains the following sterile components:”

4 CONCLUSION

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Clearside so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xipere that Clearside Biomedical, Inc. submitted on December 19, 2018.

Table 4. Relevant Product Information for Xipere (triamcinolone acetonide)	
Initial Approval Date	N/A
Active Ingredient	Triamcinolone acetonide
Indication	For the treatment of macular edema associated with uveitis.
Route of Administration	Suprachoroidal
Dosage Form	Injectable suspension
Strength	40mg/mL
Dose and Frequency	4 mg (0.1 mL of 40 mg/mL) injected suprachoroidally once
How Supplied	Each **XIPERE** carton contains a single-dosing tray with: 1. One single-dose glass vial of triamcinolone acetonide suprachoroidal injectable suspension 40 mg/mL 2. Sterile components for administration, sealed in a Tyvek-covered tray: • One SCS Microinjector® syringe with vial adapter attached • One 30-G x 900-µm needle • One 30-G x 1100-µm needle
Storage	Store at 15° to 25°C (59° to 77°F); do not freeze. The drug vial should be protected from light by storing in the carton.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Xipere labels and labeling submitted by Clearside Biomedical, Inc. on December 19, 2018.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

Carton Labeling:

(b) (4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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