

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208845Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | | |
|---|---|---|
| NDA # 208845 | NDA Supplement #: S- BLA Supplement #: S- | Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10) |
| Proprietary Name: Zilretta | | |
| Established/Proper Name: triamcinolone acetonide extended-release | | |
| Dosage Form: suspension for injection | | |
| Strengths: 40 mg/5 mL | | |
| Route(s) of Administration: intra-articular injection | | |
| Applicant: Flexion, Inc. | | |
| Agent for Applicant (if applicable): | | |
| Date of Application: 12/8/16 | | |
| Date of Receipt: 12/8/16 | | |
| Date clock started after Unacceptable for Filing (UN): | | |
| PDUFA Goal Date: 10/8/17 | Action Goal Date (if different): 10/6/17 | |
| Filing Date: 2/6/17 | Date of Filing Meeting: 1/18/17 | |
| Chemical Classification (original NDAs only) : | | |
| <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination | | |
| <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination | | |
| <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination | | |
| <input type="checkbox"/> Type 4- New Combination | | |
| <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer | | |
| <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA | | |
| <input type="checkbox"/> Type 8- Partial Rx to OTC Switch | | |
| <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) | | |
| <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval) | | |
| Proposed indication(s)/Proposed change(s): for the management of osteoarthritis pain of the knee | | |
| Type of Original NDA: AND (if applicable) | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) | |
| Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> | | |
| <i>http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</i> | | |

| Review Classification: | | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher | | |
|---|--|--|----|---------|
| The application will be a priority review if: <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted | | | | |
| Resubmission after withdrawal? <input type="checkbox"/> | Resubmission after refuse to file? <input type="checkbox"/> | | | |
| Part 3 Combination Product? <input type="checkbox"/> | <input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) | | | |
| <input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | | |
| Collaborative Review Division (if OTC product): | | | | |
| List referenced IND Number(s): 111325 | | | | |
| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

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|--|--|-------------------------------------|--------------------------|----------------|
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If yes, explain in comment column. | | | | |
| If affected by AIP, has OC been notified of the submission? If yes, date notified: | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i> | Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required | | | |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i> | Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears | | | |
| <u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i> | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | | | |
| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | YES | NO | NA | Comment |
| Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below: | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| • Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |

| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | | | | | | | | | | | | | | |
|--|--------------------------|-------------------------------------|------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | | | | | | | | | | | | | | |
| <ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | | | | | | | | | | | | | | |
| <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
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| <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | | | |
| <ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</p> <p>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</p> | <input type="checkbox"/> | <input type="checkbox"/> | | N/A | | | | | | | | | | | | | | | | |

| Exclusivity | YES | NO | NA | Comment |
|--|-------------------------------------|-------------------------------------|-------------------------------------|----------------|
| Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: three <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

| Format and Content | | | | |
|---|---|--------------------------|-------------------------------------|---------|
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| <p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
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| Forms and Certifications | | | | |
| <p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</p> | | | | |
| Application Form | YES | NO | NA | Comment |
| <p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <p>Are all establishments and their registration numbers listed on the form/attached to the form?</p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
|---|-------------------------------------|--------------------------|-------------------------------------|----------------|
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Debarment Certification | YES | NO | NA | Comment |
| Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
|---|-------------------------------------|-------------------------------------|-------------------------------------|----------------|
| <p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Pediatrics | YES | NO | NA | Comment |
| <p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

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| Proprietary Name | YES | NO | NA | Comment |
|--|--|--|--|---------------------------------|
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input checked="" type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included? | <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> | <input type="checkbox"/> <input type="checkbox"/> | <input type="checkbox"/> <input type="checkbox"/> | Per clinical filing rvw |
| For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

| | | | | |
|---|--|-------------------------------------|--------------------------|---|
| Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | This product has an IFU, but it is being reviewed by DMEPA in OSE, and not DRISK. |
| Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| All labeling/packaging sent to OSE/DMEPA? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | CDRH consulted for combination product |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): 9/24/13 (with DPARP) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Preliminary Cmmts issued 5/25/16, firm cancelled mtg). CMC-only pre-NDA mtg held 10/14/15 | <input type="checkbox"/> | <input type="checkbox"/> | | |
| Any Special Protocol Assessments (SPAs)? Date(s): | <input type="checkbox"/> | | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/18/17

BACKGROUND: Product is a drug-device combination product intended to be reconstituted to an extended-release suspension for intra-articular injection for the management of the pain of osteoarthritis of (b) (4). The NDA is triamcinolone acetonide and it references N 14901 (Kenalog brand of triamcinolone acetonide) which is not an extended-release product.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|-------------------------------------|--------------|---------------|-------------------------------------|
| Regulatory Project Management | RPM: | Kim Compton | Y |
| | CPMS/TL: | Matt Sullivan | Y |
| Cross-Discipline Team Leader (CDTL) | Rob Shibuya | | Y |
| Division Director/Deputy | Ellen Fields | | Y |
| Office Director/Deputy | Sharon Hertz | | Y |
| Clinical | Reviewer: | Pam Horn | Y |
| | TL: | Rob Shibuya | Y |
| Clinical Pharmacology | Reviewer: | Wei Oiu | Y |
| | TL: | Yun Xu | |
| • Genomics | Reviewer: | | |
| • Pharmacometrics | Reviewer: | | |
| Biostatistics | Reviewer: | Kate Meaker | Y |
| | TL: | David Petullo | Y |

| | | | |
|--|-----------|------------------------------------|--------|
| Nonclinical Pharmacology/Toxicology) | Reviewer: | Misol Ahn | Y |
| | TL: | Jay Chang Dan Mellon | Y Y |
| Product Quality (CMC) Review Team: | ATL: | Julia Pinto (Branch Chief) | Y |
| | RBPM: | Steve Kinsley | Y |
| • Drug Substance | Reviewer: | Sam Bain | N |
| • Drug Product | Reviewer: | Valerie Amspacher | Y |
| • Process | Reviewer: | Pei-I Chu | Y |
| • Microbiology | Reviewer: | Maria Manso | N |
| • Facility | Reviewer: | Ebern Dobbin | Y |
| • Biopharmaceutics | Reviewer: | Sandra Suarez/Haritha Mandula (TL) | Y/Y |
| • Immunogenicity | Reviewer: | | |
| • Other (e.g., Branch Chiefs, EA Reviewer) | | | |
| OMP/OMPI/DMPP (MedGuide, PPI, IFU) | Reviewer: | | |
| | TL: | | |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling) | Reviewer: | Kuong Lee | N |
| | TL: | | |
| OSE/DMEPA (proprietary name, carton/container labeling) | Reviewer: | Millie Shah | N |
| | TL: | Vicky Borders-Hemphill | Y |

| | | | |
|---|-------------------------------|--------------|---|
| OSE/DRISK (REMS) | Reviewer: | | |
| | TL: | Kim Lehrfeld | Y |
| Bioresearch Monitoring (OSI) | Reviewer: | Damon Green | N |
| | TL: | | |
| Other reviewers/disciplines: Keith Marin, CDRH Reviewer and Alan Stevens, CDRH TL (did not attend) | | | |
| Other attendees | Laurelle Cascio, DPV, OSE | | Y |
| | Denise Johnson-Lyles, DPMH PM | | Y |
| | Carrie Ceresa, DMPH Rvwr | | Y |
| | Miriam Dinitale, DPMH TL | | Y |

FILING MEETING DISCUSSION:

| | |
|---|--|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO The firm claims that bridge is that the product is bioavailable to the reference product (per clinical filing rvw.) |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments |

| | |
|---|--|
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: |
| <ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

| | |
|--|---|
| CLINICAL PHARMACOLOGY Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| BIOSTATISTICS Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter |
| PRODUCT QUALITY (CMC) Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments: per CMC filing rvw | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
|--|--|
| <p>Facility/Microbiology Review (BLAs only)</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? | <input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? | |
| <ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | <input type="checkbox"/> YES <input type="checkbox"/> NO |

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Sharon Hertz

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

| | |
|--------------------------|--|
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input type="checkbox"/> | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p> |

ACTION ITEMS

| | |
|-------------------------------------|--|
| <input type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug). |
| <input type="checkbox"/> | If RTF, notify everyone who already received a consult request, OSE PM, and RBPM |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | If priority review, notify applicant in writing by day 60 (see CST for choices) |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input checked="" type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input type="checkbox"/> | Update the PDUFA V DARRTS page (for applications in the Program) |
| <input type="checkbox"/> | Other |

Annual review of template by OND ADRA completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
10/04/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: October 3, 2017

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 208845

Product Name and Strength: Zilretta (triamcinolone acetonide extended-release injectable suspension), 32 mg per vial

Applicant/Sponsor Name: Flexion Therapeutics, Inc.

Submission Date: September 20, 2017

OSE RCM #: 2017-103-1

DMEPA Safety Evaluator: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label, diluent label, carton labeling, and Instructions for Use (IFU) for Zilretta (triamcinolone acetonide extended-release injectable suspension) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label, diluent label, carton labeling, and Instructions for Use (IFU) for Zilretta are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Shah M. Label and Labeling Review for Zilretta (NDA 208845). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 26. RCM No.: 2017-103.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILLIE C BRAHMBHATT
10/03/2017

OTTO L TOWNSEND
10/03/2017

505(b)(2) ASSESSMENT

| Application Information | | |
|---|----------------------|---|
| NDA # 208845 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: Zilretta | | |
| Established/Proper Name: triamcinolone acetonide extended-release | | |
| Dosage Form: suspension for injection | | |
| Strengths: 32 mg/5 mL | | |
| Applicant: Flexion, Inc | | |
| Date of Receipt: 12/8/16 | | |
| PDUFA Goal Date: 10/8/17 | | Action Goal Date (if different): 10/6/17 |
| RPM: Kim Compton | | |
| Proposed Indication(s): management of osteoarthritis pain of the knee | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph) | Information relied-upon (e.g., specific sections of the application or labeling) |
|---|---|
| Published literature | A literature review was provided to determine if any new nonclinical data have been published that would alter the animal reproductive and developmental information in Sections 8 and 13 of the proposed product labeling. |
| NDA 014901 Kenalog-40 | FDA’s previous finding of safety and effectiveness |

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The sponsor conducted a relative BA study between Zilretta and the listed drug, Kenalog-40, and demonstrated the systemic triamcinolone exposure of Zilretta is lower than the listed drug. Therefore, the sponsor may rely on the systemic safety findings of the listed drug. The Sponsor conducted their own clinical trial to demonstrate efficacy of Zilretta.

Reference to published studies on triamcinolone to summarize the published reproductive and developmental literature or other toxicology data potentially relevant to the safety profile of the drug product was required by the Agency as part of the standard review process. The published studies we reviewed did not test the drug product, as most toxicology studies do not test the drug product. However, the published studies did test the drug substance which is in the drug product and which is what the fetus would be exposed. Therefore, the data are directly relevant to the risk assessment for the drug substance. The drug doses employed in the published studies were compared to the maximum daily dose that would be obtained in humans utilizing a body surface area comparison. This approach is scientifically justified and an acceptable means of dose comparison across species when exposure data are not available.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Listed Drug | NDA # | Did applicant specify reliance on the product? (Y/N) |
|---------------------|--------|--|
| Kenalog-40 | 014901 | Y |

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?
YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This product is intended to have an extended duration of action and is to be administered only via the intra-articular route (the referenced product is approved for both intramuscular and intra-articular routes.)

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES NO

If “**NO**” to (a) proceed to question #11.

If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Kenalog-40 (N 014901)

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

KIMBERLY A COMPTON
10/05/2017

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

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

Memorandum

Date: August 26, 2017

To: Kimberly Compton, RPh
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Koungh Lee, RPh, MSHS
Regulatory Review Officer
Division of Advertising & Promotion Review 1 (DAPR1)
Office of Prescription Drug Promotion (OPDP)

CC: Olga Salis, Senior Regulatory Project Manager
OPDP

Subject: NDA 208845
ZILRETTA (triamcinolone acetonide for extended-release-injectable suspension), for intra-articular use
Professional Labeling Review

As requested in DAAAP's consult dated January 25, 2017, OPDP has reviewed the draft prescribing information and information for use labeling for ZILRETTA (triamcinolone acetonide for extended-release-injectable suspension), for intra-articular use. The draft prescribing information (substantially complete prescribing information) was provided to OPDP on August 22, 2017, and the information of use labeling on August 23, 2017, via email by Kimberly Compton with the file names [\\Fdfs01\ode2\DAAAP\NDA and sNDA\NDA 208845 \(Zilretta \(triamcinolone ER\) Flexion\)\Labeling\N 208-845 working copy of PI \(7-21-17\) -- USE FOR EDITS.docx](#) and [\\fdfs01\ODE2\DAAAP\NDA and sNDA\NDA 208845 \(Zilretta \(triamcinolone ER\) Flexion\)\Labeling\N 208845 IFU WORD copy from firm 8-22-17.docx](#), respectively.

OPDP has provided comments on the substantially complete prescribing information in the attached document below.

OPDP has no comments on the information for use labeling.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KOUNG U LEE
08/26/2017

Clinical Inspection Summary

| | |
|-----------------------------------|--|
| Date | August 23, 2017 |
| From | Damon Green, M.D., M.S., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI) |
| To | Kimberly Compton, RPh, Sr. Regulatory Project Manager Pamela Horn, M.D., Clinical Reviewer Robert Shibuya, M.D., Clinical Team Lead Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| NDA/BLA # | 208845 |
| Applicant | Flexion Therapeutics Inc. |
| Drug | Zilretta™ (Triamcinolone Acetonide ER for Injection) |
| NME (Yes/No) | No |
| Therapeutic Classification | Synthetic Corticosteroid |
| Proposed Indication(s) | Management of osteoarthritis (OA) pain in [REDACTED] (b) (4) |
| Consultation Request Date | March 10, 2017 |
| Summary Goal Date | August 25, 2017 |
| Action Goal Date | October 8, 2017 |
| PDUFA Date | October 8, 2017 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Dr. Maria Fernandez and Dr. Quang Vo were inspected in support of this NDA. The final classification of both inspections was NAI. Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective application.

Observations for the clinical site of Dr. Vo are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

II. BACKGROUND

Flexion Therapeutics, Inc., sponsor of NDA 208845 is seeking approval for Triamcinolone Acetonide (Zilretta™) Injectable Suspension for the management of osteoarthritis (OA) pain in

(b) (4)

Inspections were requested for study **Protocol FX006-2014-008** entitled, “A Double-Blind, Randomized, Single-Dose Study to Assess the Safety and Efficacy of FX006 for the Treatment of Pain in Patients with Osteoarthritis of the Knee,” The sites chosen - Dr. Fernandez and Dr. Vo - had never been inspected. Dr. Vo had the highest number of enrolled subjects; Dr. Fernandez had a high rate of treatment responders.

Subjects were screened at 41 study centers worldwide, including the United States, Canada, Australia, New Zealand, Hong Kong, and the European Union. A total of 486 patients were randomized. The first patient enrolled on January 29, 2015, and the last patient completed the study on January 21, 2016.

The primary efficacy endpoint is reduction in pain as measured by the change from baseline to Week 12 in the weekly mean of the average daily (24 hour) pain intensity scores (as reported by patients based on the 11-point Numeric Rating Scale (NRS)). The sponsor concluded that at Week 12, the reduction from baseline in average daily pain scores was significantly greater in the 40 mg FX006 group than in the placebo group (-3.1 versus -2.1, respectively; 2-sided $p < 0.0001$); thus, the primary endpoint was met, constituting a large and clinically relevant effect relative to baseline.

III. RESULTS (by site):

| Name of CI, Address, Country if non-U.S. or City, State if U.S. | Protocol #, Site #, and # of Subjects | Inspection Date | Classification |
|---|--|---------------------------|--|
| Maria C. Fernandez, M.D. Finlay Research Clinic 1140 West 50 th Street, Suite 406 Hialeah, FL 33012 | Protocol: FX006-2014-008 Site: 66 Subjects: 40 | 07/24/2017- 07/28/2017 | NAI |
| Quang D. Vo, M.D. Dream Team Clinical Research 760 North Euclid, Suite 105 Anaheim, CA 92801 | Protocol: FX006-2014-008 Site: 33 Subjects: 40 | 7/31/2017 – 8/03/2017 | Pending; Interim Classification: NAI |

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations; Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Maria C. Fernandez

Dr. Fernandez is a board certified Physician in Family Practice, and maintains her licensure in the state of Florida. Under Protocol FX006-2014-008, 55 subjects were screened, 40 subjects were enrolled, with all 40 completing the study. The number of subject records reviewed during the inspection included 28 of the enrolled subjects and 15 of the screening failures (43 total records). The inspection covered a review of all available records as follows: informed consents; protocol amendments; signed investigator agreement, Financial Disclosure Statements; IRB submissions and correspondence; adverse events reporting; clinical source data, including subject evaluations; investigational drug product accountability and monitoring; concomitant drugs; and sponsor monitoring activities.

There were no significant observations made during the inspection; therefore no FDA-483 was issued.

Overall, the study appears to have been conducted without violation in data integrity or subject safety and well-being. The data generated by this site appears acceptable in support of this current application.

2. Dr. Quang D. Vo

The inspection is complete though the EIR is pending. Preliminary communication from the inspector reveals no significant regulatory violations were found, and no FDA-483 was issued.

{See appended electronic signature page}

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Shibuya
DAAAP /Project Manager/ Compton
DAAAP/Medical Officer/Horn
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Thompson
OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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/s/

DAMON C GREEN
08/23/2017

SUSAN D THOMPSON
08/24/2017

KASSA AYALEW
08/24/2017

Consult Question:

The Sponsor submitted a white paper in support of the proposed section 8 pregnancy and lactation labeling. DAAAP requests that DPMH review and provide input on what the sponsor proposed. Please provide guidance in the review of that portion of the label.

INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of Zilretta (triamcinolone acetonide) ER intra-articular (IA) injection labeling.

REGULATORY HISTORY

On December 8, 2016, Flexion submitted a New Drug Application (NDA) for Zilretta (triamcinolone acetonide) extended release (ER) injection for the management of osteoarthritis pain of [REDACTED] (b) (4) NDA 208845 is a 505(b)(2) application relying on the safety and efficacy of the reference listed drug (RLD) Kenalog-40 (triamcinolone acetonide) injection suspension (NDA 14901).

- NDA 14901, Kenalog-40, originally approved on February 1, 1965
 - Kenalog-40 is indicated for intra-articular or soft tissue administration for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis or osteoarthritis

BACKGROUND**Drug Characteristics**^{1,2,3}

- Triamcinolone acetonide is a synthetic glucocorticoid corticosteroid with anti-inflammatory properties.
 - The anti-inflammatory activity of corticosteroids is due to the decrease of inflammatory transcription factors and regulation of post-transcriptional pathways. Specifically, corticosteroids, such as triamcinolone, inhibit the transcription of cytokines that are prevalent in the inflammation of osteoarthritis.
- Zilretta is an extended release dosage form consisting of microspheres of poly(lactic-co-glycolic acid) (PLGA) containing triamcinolone acetonide and is administered by intra-articular injection.
 - Following intra-articular injection, triamcinolone is released to the synovial tissues from the microspheres over a period of approximately 3 months.
- See the table below for a comparison of Zilretta, immediate release triamcinolone acetonide for intra-articular injection and oral, inhaled and intravenous formulations of triamcinolone acetonide:

¹ 7/3/2014. FDA Approved Package Insert for Reference Listed Drug. Kenalog-40. NDA 14901

² Applicant proposed labeling for Zilretta, NDA 208845

³ Derendorf, et al. Pharmacokinetics of Triamcinolone Acetonide After Intravenous, Oral, and Inhaled Administration. The Journal of Clinical Pharmacology. 1995; 35: 302-305.

Table 1. Triamcinolone Drug Characteristics*

| Drug Characteristics | Zilretta | Triamcinolone Acetonide intra-articular injection (immediate-release) | Triamcinolone Acetonide (oral) | Triamcinolone acetonide (inhaled) | Triamcinolone Acetonide (intravenous) |
|--|-----------------|--|---------------------------------------|--|--|
| Molecular Weight | 434.50 Daltons | 434.50 Daltons | 434.50 Daltons | 434.50 Daltons | 434.50 Daltons |
| T_{1/2} (hours) | 633.9 | 146.9 | 2.6 | 3.6 | 2 |
| C_{max} (pg/mL) | 1,143.7 | 21,062.2 | 10,500 | 2,000 | |
| AUC_{0-24 hour} (pg•h/mL) | 21,219.2 | 297,545.3 | 30,400 | 11,900 | 57,700 |

*Reviewers table adapted from information provided by the applicant and Deredorff et al (1995)³

- After treatment with Zilretta, plasma pharmacokinetic analyses showed lower peak systemic exposure (C_{max}) and lower overall exposure relative to immediate release triamcinolone acetonide for intra-articular injection and oral, inhaled and intravenous formulations of triamcinolone acetonide
- Regarding the Area-Under-the Curve (AUC), the AUC_{0-24 hour} for Zilretta is lower than immediate release triamcinolone acetonide for intra-articular injection, oral and intravenous triamcinolone acetonide and higher than inhaled triamcinolone acetonide.
- Most common side effects include: arthralgia, headache, joint swelling, back pain, nasopharyngitis, upper respiratory tract infection and confusion

Osteoarthritis^{4,5}

There are no professional guidelines available on osteoarthritis and pregnancy. Although osteoarthritis can occur in all ages, it is most common in individuals over the age of 65.

Osteoarthritis has the following characteristics:

- Most common form of arthritis
- Causes damage to the articular cartilage
- Can occur in any joint in the body but most commonly affects the joints in the knees, hips, spine and hands
- Symptoms are worse after a period of rest
- Treatment options include: physical therapy, regular exercise, acetaminophen, NSAIDs, opioids, corticosteroid injections, hyaluronic acid injection or joint replacement as last resort.

⁴ Sinusas, K, 2012, Osteoarthritis: Diagnosis and Treatment, Am Fam Physician, 85(1):49-56.

⁵ What is Osteoarthritis. Arthritis Foundation. <http://www.arthritis.org/about-arthritis/types/osteoarthritis/what-is-osteoarthritis.php>. Accessed 21 April 2017.

Current State of the Labeling

The current labeling for Kenalog-40, the RLD, is not in PLR or PLLR format. The following is noted with labeling for the RLD:

- There is no boxed warning for embryofetotoxicity or a contraindication for pregnancy or lactation.
- There are no human data regarding pregnancy. There is general information about the effects of corticosteroids in pregnant animals and an increased incidence of cleft palate.
- There is no existing pregnancy testing or contraception recommendation.
- There is no known drug-drug interaction with hormonal contraception.

REVIEW

PREGNANCY

Nonclinical Experience

Reproductive toxicology studies with triamcinolone in animals have not been conducted. From published literature, in animal reproductive studies in pregnant mice, rats, rabbits, or primates, triamcinolone acetate caused resorptions, decreased fetal body weight, craniofacial and/or other abnormalities following administration of doses that produced exposures less than the maximum recommended human daily dose (MRHDD) on a mg/m² or AUC basis. The reader is referred to the Pharmacology/Toxicology review by Misol Ahn, Ph.D.

Review of Literature^{6,7,8,9,10,11}

Applicant's Review of Literature

The applicant submitted a summary of published literature with regard to triamcinolone and corticosteroid exposure during pregnancy. Search parameters were not provided. See Appendix A for summary tables of the applicant's literature submission deemed relevant for the purposes of this review.

Corticosteroids have been used in pregnant women for a variety of indications for decades. Only a few conditions and clinical situations, such as asthma, allografts and lupus, require treatment throughout the entire pregnancy. According to limited published literature, corticosteroids, such as triamcinolone, demonstrate the possible risk of oral clefts with first-trimester exposure; however, three national cohort studies demonstrated no increased risk of oral clefts with corticosteroid exposure during pregnancy. The applicant provided a table of the epidemiological

⁶ Gotestam Skorpen, C and M Hoeltzenbein, et al, 2016, The EULAR points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation, *Ann Rheum Dis*, 75:795-810.

⁷ Makol, A, K Wright, and S Amin, 2011, Rheumatoid Arthritis and Pregnancy, *Drugs*, 71(15): 1973-1987.

⁸ Katz, V, Throp J, et al, 1990, Severe asymmetric intrauterine growth retardation associated with the topical use of triamcinolone, *J Obstet Gynecol*, 162:396-7.

⁹ Reinisch, J, et al, 1978, Prenatal Exposure to Prednisone in Humans and Animals Retards Intrauterine Growth, *Science*, 202: 436-438.

¹⁰ Bamfo, J, and A Odibo, 2011, Diagnosis and Management of Fetal Growth Restriction, *Journal of Pregnancy*, 1-15.

¹¹ Skuladottir, H et al, 2014, First-trimester non-systemic corticosteroid use and the risk of oral clefts in Norway, *Ann Epidemiol*, 24(9):635-640.

studies conducted using various corticosteroids use during early pregnancy and the risk of an infant with orofacial cleft (see Appendix A Table 4).^{12,13,14,15,16,17,18,19,20,21,22}

Additionally, several publications suggest that there may be an increased risk of intrauterine growth restriction (IUGR) in fetuses exposed to corticosteroids during pregnancy; however, in one retrospective analysis triamcinolone was favorable to other corticosteroids with regard to birth weight even though the results were not significantly different (see Appendix B Table 3).^{17,23,24} A fetus is diagnosed with IUGR when their estimated weight is below the 10th percentile for gestational age. IUGR occurs in approximately 5-10% of all pregnancies and can be associated with perinatal morbidity and mortality. Neonates with IUGR can suffer from respiratory difficulties, polycythemia, hypoglycemia, intraventricular hemorrhage and hypothermia. The mechanism of action of glucocorticoids and the possible cause of IUGR is not clear. There is not enough evidence to inform a drug associated risk.

DPMH's Review of Literature

DPMH performed a search of Micromedex, PubMed and Embase using the following search terms: "triamcinolone" and "pregnancy" and "fetal malformations" or "miscarriage." Those publications found in addition to the applicant's submitted literature are summarized below.

Nakamura (2006)²⁵ includes a case report of a 33 year-old female in Japan at 16 weeks gestation who presented with bilateral serous retinal detachments associated with anterior chamber inflammation. The patient was diagnosed with Vogt-Koyanagi-Harada (VKH) disease and was treated with bilateral sub-Tenon triamcinolone acetate injection. The triamcinolone dose was 20 mg in 0.5 mL. Inflammation and visual acuity resolved in two weeks. No occurrence of

¹² Skuladottir, H, et al, 2014, Corticosteroid Use and Risk of Orofacial Clefts, Birth Defects Research (Part A) 100: 499-506.

¹³ Ching-Chi, C, et al. 2013, Pregnancy Outcomes After Maternal Exposure to Topical Corticosteroids: A UK Population-Based Cohort Study, JAMA Dermatol, 149(11):1274-1280.

¹⁴ Hviid, A, and D Mølgaard-Nielsen, Corticosteroid use during pregnancy and risk of orofacial clefts, CMAJ, 183(7), 796-804.

¹⁵ Carmichael, S, et al, 2007, Maternal corticosteroid use and orofacial clefts, AJOG, 197:585.e1-585.e7.

¹⁶ Kallen B, 2003, Maternal Drug Use and Infant Cleft/Lip Palate with Special Reference to Corticoids, Cleft Palate-Craniofacial Journal, 40(6): 624-628.

¹⁷ Edwards, M, et al, 2003, Case-Control Study of Cleft Lip or Palate After Maternal Use of Topical Corticosteroids During Pregnancy, American Journal of Medical Genetics, 120A:459-463.

¹⁸ Pradat, P, et al, 2003, First Trimester Exposure to Corticosteroids and Oral Clefts, Birth Defects Research (Part A), 67:968-970.

¹⁹ Park-Wyllie, L, et al, Birth Defects After Maternal Exposure to Corticosteroids: Prospective Cohort Study and Meta-Analysis of Epidemiological Studies, Teratology, 62:385-392.

²⁰ Carmichael, S, and G Shaw, 1999, Maternal Corticosteroid Use and Risk of Selected Congenital Anomalies, American Journal of Medical Genetics, 86:242-244.

²¹ Rodriguez-Pinilla, E, and M Martinex-Frias, 1998, Corticosteroids During Pregnancy and Oral Clefts: A Case-Control Study, Teratology, 58:2-5.

²² Czeizel, A, and M Rockenbauer, 1997, Population-Based Case-Control Study of Teratogenic Potential of Corticosteroids, 56:335-340.

²³ Dombrowski, M, et al, 1999, Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy. J Allergy Clin Immunol, 103(2):S356-S359.

²⁴ Rahimi, R, et al, 2006, Meta-analysis funds use of inhaled corticosteroids during pregnancy safe: a systemic meta-analysis review, Huma & Experimental Toxicology, 25:447-452.

²⁵ Nakamura, T, et al, 2016, Sub-Tenon Triamcinolone Acetonide Injection In A Pregnant Patient With Vogt-Koyanagi-Harada Disease, Retinal Cases & Brief Reports, 0:1-4.

inflammation occurred over next 13 months. Patient delivered a healthy baby boy at 41 weeks gestation. Vogt-Koyanagi-Harada disease is usually treated with high doses of corticosteroids.

In another case report by Doi (2000)²⁶ at the Department of Ophthalmology at Mie University School of Medicine in Mie, Japan, a 26 year-old female at 16 weeks gestation was diagnosed with VKH and treated with prednisolone at 18 weeks gestation. The patient delivered at 37 weeks gestation with low-birth-weight, epibulbar dermoid, lipodermoids and preauricular appendages. The authors concluded that the infant's anomalies were attributed to genetics rather than the corticosteroids and VKH disease.

In another case report by Fazelat (2011)²⁷ a 23 year-old female with type 1 diabetes at six weeks gestation presented with blurred vision and diagnosed with macular edema and retinopathy was treated with triamcinolone acetonide injection. The dose of intravitreal triamcinolone was 0.05 mL from a 40 mg/mL injection in both eyes. A healthy baby was delivered at full term.

Summary

There is evidence of embryofetal toxicity in animal reproduction studies from published literature with corticosteroid use during pregnancy; however, no formal animal reproduction studies have been conducted with triamcinolone injection. Human data from published literature for corticosteroids have produced inconsistent findings with respect to fetal malformations and are not sufficient to inform a potential risk to the fetus. Although some studies reported an increased risk of cleft lip, cleft palate, intrauterine growth restriction and decreased birth weight, other studies reported no increased risk. Methodological limitations of these studies, including small sample size, recall bias, lack of information regarding dose and timing of exposure and concomitant use of other medications, preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of corticosteroids in pregnancy. The applicability of the findings from published studies with corticosteroid exposure in pregnancy to a single intraarticular injection of triamcinolone is limited as inhaled, topical and oral corticosteroids are the most common dosage forms referenced in the available published literature.

In addition, compared to other formulations of triamcinolone acetonide (oral, inhaled, intravenous), Zilretta, has lower peak systemic exposure. See **Drug Characteristics** above for further details.

LACTATION

Nonclinical Experience

There are no formal nonclinical studies with triamcinolone with regard to lactation. There are nonclinical data referenced in published literature that demonstrate that exogenous glucocorticoids may diminish milk production and milk ejection in several different species. The reader is referred to the Pharmacology/Toxicology review by Misol Ahn, Ph.D.

²⁶ Doi, M, et al, 2000, Vogt-Koyanagi-Harada syndrome in a pregnant patient treated with high-dose systemic corticosteroids, *Acta Ophthalmologica Scandinavica*, 78:93-96.

²⁷ Fazelat, A, and K, Lashkari, 2001, Off-label use of intravitreal triamcinolone acetonide for diabetic macular edema in a pregnancy patient. *Clinical Ophthalmology*, 5:439-441/

Review of Literature^{28,29,30}

Applicant's Review of Literature

There is limited published literature on the use of corticosteroids during lactation. The applicant notes that systemically administered corticosteroids appear in human milk. Several articles reference the use of endogenous corticosteroids and delayed lactogenesis, lower than average milk volumes and suppression of lactation. See Appendix A for more specific publication details.

DPMH's Review of Literature

DPMH performed a search of Medications and Mother's Milk³¹, the Drug and Lactation Database (LactMed)³², and Micromedex³³ and a search in PubMed using the search terms "triamcinolone" and "breastfeeding" or "lactation." The results of that search are described below. The Micromedex and PubMed results did not furnish additional information.

In Medications and Mother's Milk, Dr. Thomas Hale, a breastfeeding expert, notes the following:

Although no data are available on triamcinolone secretion into human milk, it is likely that the milk levels would be exceedingly low and not clinically relevant when administered via inhalation or intranasally. There is virtually no risk to the infant following the intranasal or aerosol products in breastfeeding mothers.

*Reviewer comment: There is no information in Medication and Mothers' Milk about the presence of triamcinolone in human milk after intra-articular injection, or about the possible effect on milk production as described in literature. However, based on the information reviewed above in **Drug Characteristics**, Zilretta has lower peak systemic exposure compared to other formulations (oral, intravenous, inhaled) of triamcinolone acetamide.*

LactMed describes the cases from published literature that were also submitted by the applicant and described in detail in Appendix A. In addition, LactMed states the following:

Local injections, such as for tendinitis, would not be expected to cause any adverse effects in breastfed infants, but may occasionally cause temporary loss of milk supply.

²⁸ McGuire, E, 2012, Sudden loss of milk supply following high-dose triamcinolone (Kenacort) injection, Breastfeeding Review, 20(1):32-34.

²⁹ Henderson, J, et al, 2008, Effect of preterm birth and antenatal corticosteroid treatment on lactogenesis II in women, Pediatrics, 121(1):e92-e100.

³⁰ Babwah, T, et al, 2013, An unexpected temporary suppression of lactation after a local corticosteroid injection for tenosynovitis, European of General Practice, 19:248-250.

³¹ Hale, Thomas, Ph.D., Medications and Mother's Milk 2017, Springer Publishing Company.

³² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

³³ www.Micromedexsolutions.com. Accessed 5/15/2017.

Summary

Although there are no formal clinical or non-clinical studies on triamcinolone injection in lactating women, limited published literature in humans and several animal species indicate that corticosteroids may have a temporary effect on milk production and supply.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Carcinogenicity, mutagenicity and fertility studies have not been conducted with Zilretta. The reference listed drug label does state that, “steroids may increase or decrease motility and number of spermatozoa in some patients.” The applicant provided a review of published literature on animal exposure to triamcinolone and the effects on fertility. The reader is referred to the Pharmacology/Toxicology review by Misol Ahn, Ph.D.

Review of Literature

The applicant performed a review of available published literature with regard to triamcinolone and the effects on sperm of fertility and concluded that no studies were identified in humans. DPMH performed a literature review in PubMed using the key search words “triamcinolone” and “infertility” and “males/females.” There are no published data on the use of triamcinolone injection and its effects on fertility.

Summary

Overall, no fertility studies were performed in animals and there are no published data on the use of triamcinolone and its effects on fertility in humans. (b) (4)

CONCLUSIONS

The Pregnancy and Lactation subsections of Zilretta labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” subsection of labeling was formatted in the PLLR format to include: the “Risk Summary” section.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

Published studies on the association between corticosteroids and fetal outcomes have reported inconsistent findings and have important methodological limitations. The majority of published literature with corticosteroid exposure during pregnancy includes the oral, topical and inhaled dosage formulations; therefore, the applicability of these findings to a single intraarticular injection of triamcinolone acetonide is limited. In animal reproductive studies from published literature, pregnant mice, rats, rabbits, or primates administered triamcinolone acetonide during the period of organogenesis at doses that produced exposures less than the maximum recommended human dose (MRHD) caused resorptions, decreased fetal body weight, craniofacial and/or other abnormalities such as omphalocele (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant mice dosed with triamcinolone acetonide via intramuscular or subcutaneous injection at doses equivalent to (b) (4) times the MRHD (b) (4) or higher caused cleft palate and a higher rate of resorption. In pregnant rats dosed with triamcinolone acetonide via intramuscular or subcutaneous injection at doses equivalent to 0.3 times the MRHD (b) (4) or higher caused developmental abnormality (cleft palate, omphalocele, late resorption, and growth retardation) and fetal mortality. No notable maternal toxicity was observed in rodents. Pregnant rabbits dosed with triamcinolone via intramuscular injection for 4 days at doses equivalent to 0.15 times the MRHD (b) (4) or higher caused resorption and cleft palate. No notable maternal toxicity was observed.

Pregnant primates dosed with triamcinolone via intramuscular injection for 4 days at doses equivalent to 3 times the MRHD (b) (4) or higher caused severe craniofacial CNS and skeletal/visceral malformation and a higher prenatal death. No notable maternal toxicity was observed.

8.2 Lactation

Risk Summary

There are no available data on the presence of triamcinolone acetonide in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. However, (b) (4) corticosteroids have been detected in human milk and may suppress milk production. It is not known whether intra-articular administration of ZILRETTA could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZILRETTA and any potential adverse effects on the breastfed infant from ZILRETTA or from the underlying maternal condition.

Appendix A. Summary of Applicant's Published Literature on Corticosteroid/Triamcinolone Exposure During Pregnancy and Lactation

Table 1. Review Articles: Corticosteroids/Triamcinolone Exposure During Pregnancy

| Publication | Country | Prospective or Retrospective Data – study type | Maternal Exposure (dose/duration) | Total Pregnancies | Other Meds | Mother's OB history | Miscarriages | Congenital Abnormality | Conclusion |
|--------------------------------------|----------------------------|--|--|--|------------|---------------------|----------------|--|--|
| Götestam Skorpen (2016) ⁶ | Europe – various countries | Retrospective – review article – search period from 2008 to 2015 – for glucocorticoids, 2 cohorts, 5 case controls and 17 case reports were identified | Glucocorticoids – any route/formulation not specified | 3500 - 94 prospective and 3406 retrospective | Unknown | Unknown | 70/331 (21.1%) | 34/3180 (1.1%) | Miscarriages high however author concluded confounding by rheumatic disease; congenital abnormalities no difference compared to controls |
| Rahimi (2006) ²⁴ | Unknown | Meta-analysis of pooled data from all clinical studies in women exposed to inhaled corticosteroids during pregnancy from 1997-2005 (4 studies total) | Inhaled fluticasone, beclomethasone, budesonide, triamcinolone and flunisolide | Unknown | Unknown | Asthma | Not reviewed | OR 0.96 with a CI of 0.51-1.83 for the two studies that captured major malformations with a P value 0.9582 | Results conclude that inhaled corticosteroids do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy induced hypertension |

Table 2. Case Reports/Case Series: Corticosteroids/Triamcinolone Exposure During Pregnancy and Lactation

| Publication | Subject Demographics | Maternal Exposure (dose/duration) | Estimated Fetal Exposure | Other meds | Mother's OB history | Pregnancy/Lactation Outcome | Congenital Abnormality |
|------------------------------|--|---|---|-------------|---|--|------------------------|
| Katz (1990) ⁸ | 28 year old female with atopic dermatitis | Triamcinolone 0.05% topical starting at 12 weeks gestation to legs, abdomen and extremities; calculated daily dose of triamcinolone approximately 40 mg/day | 12 weeks to 29 weeks gestation | none | Previous term pregnancy uncomplicated | Patient admitted to hospital at 29 weeks gestation when ultrasound showed normal fetus but low amniotic fluid; all lab testing normal; amniotic fluid back to normal 7 days after stopped med and patient was discharged and put on bedrest; 7 days later ultrasound showed low fluid and lack of fetal growth; cesarean section performed at 31 weeks gestation; small for gestational age but no abnormalities; 14 days after birth infant developed necrotizing enterocolitis and had surgery; patient had another child at an unknown future time point that was delivered at 34 weeks gestation at 10% weight for gestational age | None |
| McGuire (2012) ²⁸ | 35 year old female with severe thoracic and cervical spine and restricted movement in shoulder due to bursitis | Betamethasone 5.7 mg injection in shoulder and 4 weeks later 80 to 120 mg of triamcinolone into her vertebral joints | 14 month old infant still breastfeeding | Domperidone | Two previous children and abundant milk supply with both pregnancies; history of severe pain in thoracic and cervical spine during past pregnancies | Sudden decrease in milk production after injection into vertebral joints but not after initial injection into shoulder | N/A |

| | | | | | | | |
|-----------------------------|--|--|-----------------------|---------|---------|---|------|
| Babwah (2013) ³⁰ | 26 year old female; six weeks postpartum and breastfeeding | Intra-lesional injection of Methyl prednisolone acetate 24 mg and 15 mg lidocaine for treatment of De Quervain's tenosynovitis | Approximately 6 weeks | Unknown | Unknown | Lactation had ceased at about 30 hours post injection; however 36 hours later lactation had resumed | None |
|-----------------------------|--|--|-----------------------|---------|---------|---|------|

Table 3. Studies/Trials: Corticosteroids/Triamcinolone Exposure During Pregnancy and Lactation

| Publication | Country/Territory | Prospective or Retrospective Data – study type | Maternal Exposure (dose/duration) | Total Pregnancies | Other Meds | Mother's OB history | Miscarriages | Congenital Abnormality | Conclusion |
|---|----------------------------|--|--|---|------------|---------------------|--------------|------------------------|---|
| Reinisch (1978) ⁹ | United States – California | Retrospective review of women at a private southern California infertility clinical between 1955-1975 | prednisone 10 mg daily before and during pregnancy | 119 in treatment group and 67 controls who did not receive hormonal therapy | unknown | Infertility | Unknown | None | All patient delivered at full-term 38 ± 2 weeks; those infants who received prednisone weighted significantly less than those in the control group; researchers also performed a similar experiment in mice with similar results |
| Dombrowski (1999) ²³ Preliminary data from 3 types of studies | United States | Retrospective analysis of inhaled steroid use in a maternal-fetal medicine research center | Inhaled triamcinolone; inhaled beclomethasone; oral theophylline | Inhaled triamcinolone (n=16); inhaled beclomethasone (n=14); oral theophylline (n=25) | Unknown | Unknown | Unknown | None | Average birth weight in beclomethasone group was 500 g less than the triamcinolone group however not statistically significant; no differences between groups for gestational age or 5 min APGAR score; patients in the triamcinolone group had fewer hospitalizations for asthma exacerbations |
| | United States | A large observational cohort study assessing the effects of different types of asthma treatment on perinatal outcomes; | Unknown | 807 women with moderate to severe asthma; 813 women with mild asthma and 815 | Unknown | Unknown | Unknown | Unknown | study ongoing at time of publication |

| Publication | Country/Territory | Prospective or Retrospective Data – study type | Maternal Exposure (dose/duration) | Total Pregnancies | Other Meds | Mother's OB history | Miscarriages | Congenital Abnormality | Conclusion |
|--------------------------------|-------------------|--|---|---|------------|---------------------|--------------|------------------------|---|
| | | trial still ongoing at time of publication | | controls | | | | | |
| | United States | A randomized clinical trial comparing theophylline and inhaled beclomethasone in the treatment of pregnancy women with moderately severe asthma | Theophylline 40 to 800 mg daily; placebo inhaler or beclomethasone 4 puffs 3 times daily and placebo capsules; inhaled albuterol is allowed as need and oral corticosteroids for severe exacerbations | Unknown; trial ongoing at time of publication | Unknown | Unknown | Unknown | Unknown | trial ongoing at time of publication |
| Henderson (2008) ²⁹ | Australia | Women who presented to King Edward Memorial Hospital who delivered before 34 weeks gestation were enrolled to test the effect of antenatal corticosteroid treatment and pre-term birth on milk volume and expression | Betamethasone IM 11.4 mg 24 hours apart for 2 doses; n=50 (milk volume recorded for 46 women) | 46 | N/A | Unknown | N/A | N/A | Significant positive effect of gestational age on milk lactose levels; women who delivered 0-2 days after betamethasone treatment demonstrated significantly greater volumes of milk than women who delivered 3 to 9 days after treatment |

Appendix B. Applicant's Table found in Module 1.14.1.3 of the December 8, 2016, submission to NDA 208845

Table 4. Summary of Epidemiological Studies on Corticosteroid Use During Pregnancy and Risk of Orofacial Clefts

| Study (year) | Country/study design/ exposure assessment | Mode | Relative risk estimates (95% CI) | | |
|--|---|------------------------|----------------------------------|----------------------------------|----------------------------------|
| | | | All | CLP | CP |
| <i>Skuladottir et al.-2014a*</i> | Norway/ National | Any Dermatologic | 1.5 (0.8, 2.9) 2.8 (0.9–8.2) | 1.4 (0.7–2.8) 2.3 (0.7–7.7) | 1.7 (0.7–4.00) 3.4 (0.9–13.1) |
| | Case-control/ Population-based | Other Dermatologic | 1.0 (0.5–2.3) 1.0 (0.5–2.2) | 0.9 (0.4–2.4) 1.2 (0.5–2.9) | 1.1 (0.3–3.4) 0.6 (0.1–2.6) |
| | Cohort Study | | | | |
| | | | | | |
| <i>Skuladottir et al.-2014b</i> | USA/ Population-based | Any Systemic | | 1.0 (0.7, 1.4) 1.3 (0.6, 2.8) | 0.7 (0.4, 1.2) 0.9 (0.3, 2.8) |
| | Case-control/ Questionnaire | Nasal Topical | | 1.0 (0.7, 1.6) - | 0.8 (0.5, 1.6) - |
| | | | | | |
| | | | | | |
| <i>Chi et al.-2013</i> | United Kingdom/ Population-based Cohort Study/ Drug registry | Dermatologic | 1.9 (0.2–15) | | |
| <i>Hviid & Molgaard-Nielsen-2011</i> | Denmark/ Population-based | Anv Inhaled | | 1.1 (0.8, 1.4) 0.8 (0.3, 1.7) | 1.2 (0.8, 1.8) 0.9 (0.3, 2.9) |
| | Birth Cohort/ Prescription | Nasal Dermatologic | | 0.5 (0.2, 1.2) 1.5 (1.0, 2.1) | 1.1 (0.4, 2.6) 1.5 (0.9, 2.5) |
| | Drug Registry | Other topical | | 1.0 (0.6, 1.8) | 1.0 (0.4, 2.3) |
| | | | | | |
| | | | | | |
| <i>Carmichael et al.-2007</i> | USA/ Population-based | Anv Systemic | | 1.7 (1.1, 2.6) 2.1 (0.9, 4.7) | 0.5 (0.2, 1.3) 0.8 (0.2, 3.6) |
| | Case-control/ Questionnaire | Nasal Topical | | 1.5 (0.9, 2.5) 0.9 (0.2, 4.3) | 0.7 (0.1, 1.8) - |
| | | | | | |
| | | | | | |
| <i>Kallen et al.-2003</i> | Sweden/ Population-based | Anv Systemic | 1.4 (1.0, 2.0) 1.9 (0.8, 4.0) | 1.1 (0.6, 1.9) | 1.8 (0.9, 3.2) |
| | Birth Cohort/ Medical | Inhaled Nasal drops | 1.2 (0.7, 1.9) 1.4 (0.6, 2.9) | | |
| | Birth registry | Topical | 2.0 (0.6, 5.2) | | |
| | | | | | |
| | | | | | |

| | | | | | |
|--------------------------------------|--|---|--|---|---|
| <i>Edwards et al.-2003</i> | Australian/ Hospital-based Case-control/ Questionnaire | Topical | 13.2 (1.7, 586) | 11.7 (1.4, 537) | 12.0 (1.1, 600) |
| <i>Pradat et al.-2003</i> | Multi National/ 9 Birth Defect Registries Case-control | Intestinal Dermatologic Systemic Systemic combined Inhaled Nasal | 0.6 (0.1, 2.9) 0.5 (0.2, 1.6) 1.3 (0.9, 2.0) 2.1 (1.0, 4.3) 0.6 (0.2, 1.7) 1.7 (0.6, 4.3) | - 0.7 (0.2, 2.4) 1.8 (1.0, 3.1) 2.6 (1.2, 5.7) 0.7 (0.2, 2.2) 2.5 (1.0, 6.3) | 3.0 (0.7, 13) - 0.3 (0.0, 1.5) 1.2 (0.3, 4.9) 0.6 (0.1, 5.1) - |
| <i>Park-Wyllie et al.-2000</i> | Multi National/ Meta-analysis of case-control studies | Any | 3.4 (2.0, 5.7) | | |
| <i>Carmichael & Shaw-1999</i> | California, USA/Population-based Case-control/ Questionnaire | Any | | 4.3 (1.1, 17) | 5.3 (1.1, 27) |
| <i>Rodriguez-Pinilla et al.-1998</i> | Spain/ Hospital-based Case-control | Systemic | 5.2 (1.5, 17.1) | 8.9 (2.0, 38) | |
| <i>Czeizel et al.-1997</i> | Hungary/ Population-based Case-control/ Questionnaire | Oral Topical | 1.27 (0.8, 2.0) 2.21 (1.1, 4.4) | | |

*Odds ratios adjusted for mother's education, work status in early pregnancy, alcohol intake, smoking, folic acid supplementation, dietary folates, multivitamin supplementation, and calendar year of baby's birth.

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/s/

CARRIE M CERESA
08/18/2017

MIRIAM C DINATALE
08/18/2017

LYNNE P YAO
08/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CONSULTATION

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 14, 2017

FROM: Smita B. Abraham, MD, Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

THROUGH: Marina Zemskova, MD, Clinical Team Leader, DMEP
Jean-Marc Guettier, MD, Director, DMEP

TO: Kim Compton, Regulatory Project Manager, Division of Anesthesia, Analgesia,
and Addiction Products (DAAAP)

SUBJECT: Effects of intra-articular triamcinolone injection on the hypothalamic-pituitary-adrenal axis

I. DMEP Response to Consult Questions

Please review and comment on the pharmacodynamic portion of the study design and results of the following [FX006-2011-002] study and comment on the proposed labeling in Section 12.2.

First, we note that the study is quite limited. The study, for example, lacks any clinical assessment of adrenal insufficiency, did not employ dynamic cortisol testing (i.e., the standard confirmatory diagnostic test), and lacked a standardized protocol for serum cortisol collection. These limitations hinder our ability to interpret the clinical meaningfulness of the PD changes.

Overall, the data suggest systemic absorption of FX006 and some degree of acute Hypothalamic-Pituitary-Adrenal (HPA) axis suppression with all three doses of FX006 (i.e., 10 mg, 40 mg, and 60 mg). DMEP agrees with the Sponsor's conclusion that a single IA injection of FX006 results in a pattern of cortisol suppression that is dose and time-dependent with the lowest degree of suppression observed in the 10 mg group followed by higher degrees of suppression in the 40 mg and 60 mg groups, respectively.

The Sponsor seeks approval of the 40 mg dose of FX006, thus the effect on HPA axis of only 40 mg is discussed in further detail below.

Subjects who receive FX006 40 mg experience HPA axis suppression within the first 24 hours after dosing. HPA axis recovery seems to occur over 4-6 weeks following a single 40 mg dose. These data demonstrate that there is some level of HPA axis suppression and patients might be at risk for adrenal insufficiency once their systemic TCA level starts to decrease. However, accurate predictors are not available to distinguish between the patients that will become adrenally insufficient and those that will not (5). Previous clinical experience as documented in the literature and as recognized in the approved Kenalog-40 labeling identifies adrenal insufficiency as a risk associated with IA corticosteroid injections. (b) (4)

we recommend including language in labeling to address these risks.

DMEP comments on language presented in section 12.2 of the submitted label

The currently proposed language in Section 12.2 of the submitted draft label for FX006 40 mg, with regard to the HPA axis is:

Studies indicate that following a single intramuscular dose of 60 to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. To assess potential effects of the systemic levels of triamcinolone acetonide associated with a single intra-articular (IA) administration of ZILRETTA on hypothalamic pituitary adrenal (HPA) axis function, serum and urine cortisol levels were monitored over 6 weeks post injection. (b) (4)

The Division recommends deleting the statement (b) (4)

the cortisol data from FX006-2011-002 show evidence of at least mild-moderate suppression in the first few days after FX006 40 mg injection and a gradual return to normal over the course of the 6 week study. (b) (4)

The Division's recommendations are provided below in red font:

Studies indicate that following a single intramuscular dose of 60 to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. To assess potential effects of the systemic levels of triamcinolone acetonide associated with a single intra-articular (IA) administration of ZILRETTA on hypothalamic pituitary adrenal (HPA) axis function, serum cortisol levels were monitored over 6 weeks (42 days) post injection. **As with triamcinolone acetonide, adrenal suppression occurred within 12-24 hours and then gradually returned to normal, within 30-42 days.**

Additional comments:

1. The Sponsor appropriately addressed the risk of adrenal insufficiency in Warnings Section 5.6 as stated below:

5.6 [REDACTED] (b) (4)

Alterations in Endocrine Function

Corticosteroids can produce reversible hypothalamic-pituitary-adrenal axis suppression with the potential for [REDACTED] (b) (4) after withdrawal of treatment.

[REDACTED] (b) (4)

2. We have the following recommendations regarding the proposed language in Section 5.6:

- Change the term [REDACTED] (b) (4) ” to “adrenal insufficiency” in the first sentence.

- Remove the statement [REDACTED] (b) (4)

[REDACTED] (b) (4)

3. The Sponsor has appropriately addressed the endocrine adverse reactions post IA injection therapy as seen under the heading “Endocrine” in Section 6.2.

4. We have the following recommendation regarding the proposed language in Section 6.2 under the heading “Fluid and electrolyte disturbances”:

- Remove the terms [REDACTED] (b) (4) and [REDACTED] (b) (4) . [REDACTED] (b) (4)

[REDACTED]

II. Background and basis for Recommendations

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) received NDA 208845 for FX006 (Zilretta) on December 8, 2016. FX006 is an extended-release formulation of triamcinolone acetonide (TCA), a corticosteroid, for intra-articular (IA) administration that is intended to deliver TCA to the synovial and peri-synovial tissues for [REDACTED] (b) (4)

NDA 208845 is a 505(b)(2) application that relies, in part, on FDA’s previous findings of safety and effectiveness for the reference listed drug, Kenalog-40 (TCA, injectable suspension, USP). The Sponsor seeks approval for FX006 40 mg for the indication of: management of osteoarthritis pain of [REDACTED] (b) (4)

On May 16, 2017, the Division of Metabolism and Endocrinology Products (DMEP) received a consultation request from DAAAP regarding the effect of FX006 on the hypothalamic-pituitary-adrenal (HPA) axis.

Extensive clinical experience with immediate release IA corticosteroid injections suggests that transient suppression of HPA axis resulting in reductions of cortisol levels is common. These

transient reductions in cortisol levels do not often result in clinical adrenal insufficiency after withdrawal of corticosteroid treatment, a condition associated with increased morbidity and mortality. However, several cases of adrenal insufficiency as a result of IA corticosteroid injection have been reported in the literature (1, 2, 3). The true incidence of HPA axis suppression after IA corticosteroid injection is not known as most reports are from single cases and the diagnosis is thought to be under recognized.

As such, current labeling for Kenalog-40 includes adrenal insufficiency risk identifying language under “Warnings”:

General

“Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation. Kenalog-40 Injection is a long-acting preparation, and is not suitable for use in acute stress situations. To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with Kenalog-40 Injection and for a year afterwards.”

Endocrine

“Corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.”

To assess the effects of FX006 on the HPA axis, the Sponsor conducted FX-2011-002, “A double-blind, randomized, parallel group, active comparator study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects (HPA axis) of FX006 in patients with osteoarthritis of the knee”. DAAAP requests DMEP to comment on the pharmacodynamic portion, i.e. cortisol measurement, of the FX006-2011-002 study design, results, and comment on the proposed labeling in Section 12.2

III. Materials reviewed for consult

1. DAAAP’s consult request
2. NDA 208845, Study FX006-2011-002 Clinical Study Report and Dataset
3. Correspondence from Sponsor dated 7/14/2017 (response to FDA request for information)
4. Literature: PubMed search on therapeutic use and side effects of glucocorticoids, see references.

IV. DMEP Comments

Clinical Background - Adrenal Insufficiency

The hypothalamic-pituitary-adrenal (**HPA**) axis is responsible for cortisol production and ACTH stimulation of the adrenal is the primary regulator of cortisol production. Damage to any level of

the HPA axis can result in low production of cortisol, also known as, adrenal insufficiency (AI). Adrenal insufficiency can be divided into two categories, primary or central. Primary AI is due to destruction of the adrenal cortex and is much less common than central AI, which is due to deficient secretion of CRH by the hypothalamus and/or ACTH by the pituitary. Clinical signs and symptoms of both forms of AI include low blood pressure, hyponatremia, hypoglycemia, nausea, vomiting, anorexia, weight loss, fatigue, weakness, and dizziness. Primary AI is also associated with mineralocorticoid (e.g. aldosterone) deficiency unlike central AI in which this is not a concern.

Central AI is most commonly caused by exogenous (i.e. oral >> intra-articular, inhaled, topical) glucocorticoid use. Exogenous glucocorticoids can suppress corticotropin releasing hormone (CRH) and/or ACTH production from the pituitary gland leading to suppression of cortisol production from the adrenal gland. If HPA axis suppression is sustained with continuous exposure to exogenous glucocorticoids, and at some point the exogenous glucocorticoid dose reduced or drug discontinued, central adrenal insufficiency can result. In the case of IA glucocorticoid use, although the injected glucocorticoid suspension is normally confined to the IA cavity, systemic absorption has been widely recognized by the beneficial effect on other joints as well as development of HPA axis suppression and/or central adrenal insufficiency (1).

Regulatory History

During a pre-IND meeting held June 15, 2011 between the Sponsor and the Division of Pulmonary, Allergy and Rheumatology Products (DPARP, original division to which this IND was submitted), evaluation of the HPA axis was discussed. At that time, DPARP provided the following comments:

- Stated: “The Agency does not recognize [REDACTED] ^{(b) (4)} as a labeling claim, and we do not agree [REDACTED] ^{(b) (4)} However, AM cortisol and 24 hour urinary cortisol excretion would be appropriate safety assessments to incorporate in your trials.”
- Advised against the use of the term HPA axis suppression and suggested use of “HPA axis effect”
- Advised the Sponsor to review other corticosteroid product labels (e.g. topical, inhalational, intranasal) to see how information on HPA axis effect appears on the label
- Advised the Sponsor to design the evaluation of the HPA axis effect carefully to include an adequate duration of at least six weeks and an active comparator that perturbs the HPA axis.

In order to evaluate the effect of FX006 on the HPA axis the Sponsor conducted Study FX006-2011-002, which is described below.

❖ Protocol Summary

FX006-2011-002 was a double-blind, randomized, parallel-group, active comparator study design. The study was conducted in male and female patients ≥ 35 years of age with symptomatic osteoarthritis (OA) of the knee.

Twenty-four (24) participants were randomized (1:1:1:1) and treated with a single IA injection of either 10, 40, or 60 mg of FX006 or 40 mg of TCA immediate release (IR; approved Kenalog-40). Each participant was evaluated for a total of 6 weeks following a single IA injection. Following screening, safety, pharmacokinetics (PK) and pharmacodynamics (PD) were evaluated during one 48h inpatient period (Day-1 to 2), two 24h inpatient periods (Day 14-15 and Day 42-43) and seven outpatient visits (Days 3,4,5, 8 (week 1), 22 (week 3), 29 (week 4) and 36 (week 5). Study drug was administered on the morning of Day 1 after cortisol measurements were drawn.

Blood for serum cortisol was drawn as shown in Table 1.

Table 1. Schedule of serum cortisol assessments, FX006-2011-002

| Procedures | Screen ¹ | Inpatient | | | Outpatient Visits | | | | Inpatient | | Outpatient Visits ² | | | Inpatient | |
|--------------------------|---------------------|---------------------|----------------|-----------------|-------------------|-----------------|-----------------|----------------|---------------------|-----------------|--------------------------------|-----------------|----------------|---------------------|--------|
| | | Day -1 ³ | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 8 | Day 14 ³ | Day 15 | Day 22 | Day 29 | Day 36 | Day 42 ³ | Day 43 |
| Blood for Serum Cortisol | X ¹⁰ | X ⁸ | X ⁹ | X ¹⁰ | X ¹⁰ | X ¹⁰ | X ¹⁰ | X ⁸ | X ¹⁰ | X ¹⁰ | X ¹⁰ | X ¹⁰ | X ⁸ | | |

Source: Sponsor's clinical study report, page 31/55

⁸ Blood for serum cortisol measurements was collected between 7AM – 9 AM on day of admission (Time 0) and at hour 1, 2, 4, 6, 8, 12 and 24 hours following the first collection for that time period.

⁹ Blood for serum cortisol measurements and plasma drug concentration measurements was collected at Time 0 – pre-study drug administration (between 7AM – 9AM) and at 1, 2, 4, 6, 8, 12 and 24 hours post study drug administration

¹⁰ Blood for serum cortisol measurement was collected once (between 7 and 9AM)

Collections for 24 h urine free cortisol (UFC) levels were also performed. However, evaluation of 24 h UFC levels is not a recommended test for the assessment of clinically meaningful HPA axis suppression, i.e. adrenal insufficiency, as many patients with adrenal insufficiency can have normal 24 h UFC levels (4). Thus, 24 h UFC results will not be discussed here.

Patients with OA of the knee who were otherwise in good health or that had well-controlled chronic conditions (e.g. hypertension) were included.

For purposes of this consult, the eligibility criteria specifically related to HPA axis function are presented below. For the full set of eligibility criteria, please refer to Appendix 1.

Inclusion criteria

- Morning serum cortisol result within normal range¹ at Screening
- Willingness to abstain from use of the following during the study –

¹ The normal range for screening morning cortisol was 119 – 618 nmol/L (4.3 – 22.4 µg/dL). This range was provided by the laboratory where screening cortisol levels were analyzed.

- Oral, inhaled or intranasal corticosteroids
- IA corticosteroids in any joint

Exclusion criteria

- IA corticosteroid (investigational or marketed) in the index knee within 6 months of Screening
- Oral, inhaled or corticosteroids (investigational or marketed) within 1 month of Screening
- History of or active Cushing's syndrome

❖ Data Analysis

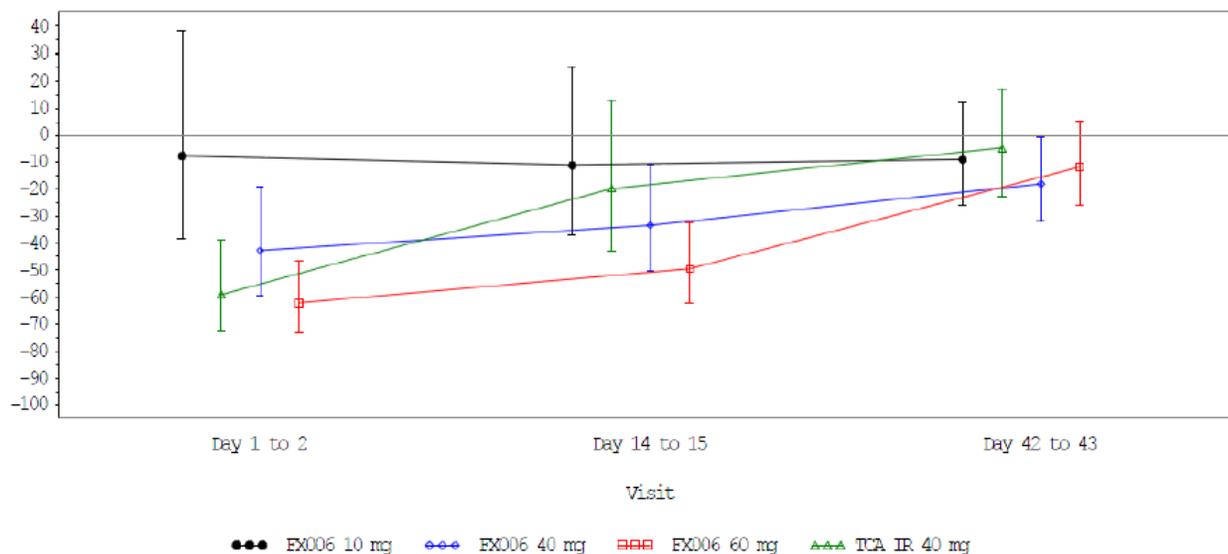
Sponsor's analysis of serum cortisol data

The primary PD endpoint was change from baseline (pre-dose) in 24-hour weighted mean serum cortisol. This is defined as the area under the curve (AUC) over the 0 to 24 hour measurement period divided by 24. This endpoint was evaluated at Days 1 to 2, Days 14 to 15 (week 2), and Days 42 to 43 (week 6). The Sponsor used this as their primary analysis to assess the effect of FX006 on HPA axis function.

All PD analyses were performed on the full analysis set (FAS) population that included all patients who received a dose of study drug and provided a baseline observation and at least one post-baseline observation. No patients had major protocol violations thus, the Per Protocol population and FAS population were the same. The minor protocol violations were reviewed and do not affect the data analysis.

Change from baseline in 24-hour weighted mean serum cortisol in each group is shown below, followed by the Sponsor's interpretation of their data (Figure 1).

Figure 1. Percent change from baseline in 24-hour weighted mean serum cortisol



1. LSMs are back transformed to obtain the ratio of on treatment response to baseline and then converted to percentage change from baseline as $(\text{ratio}-1)*100\%$ within each treatment group.

Source: Sponsor's Clinical Study Report page 61/555

Based on the data shown in Figure 1 as well as the respective tabular data (not shown here), the Sponsor concluded that:

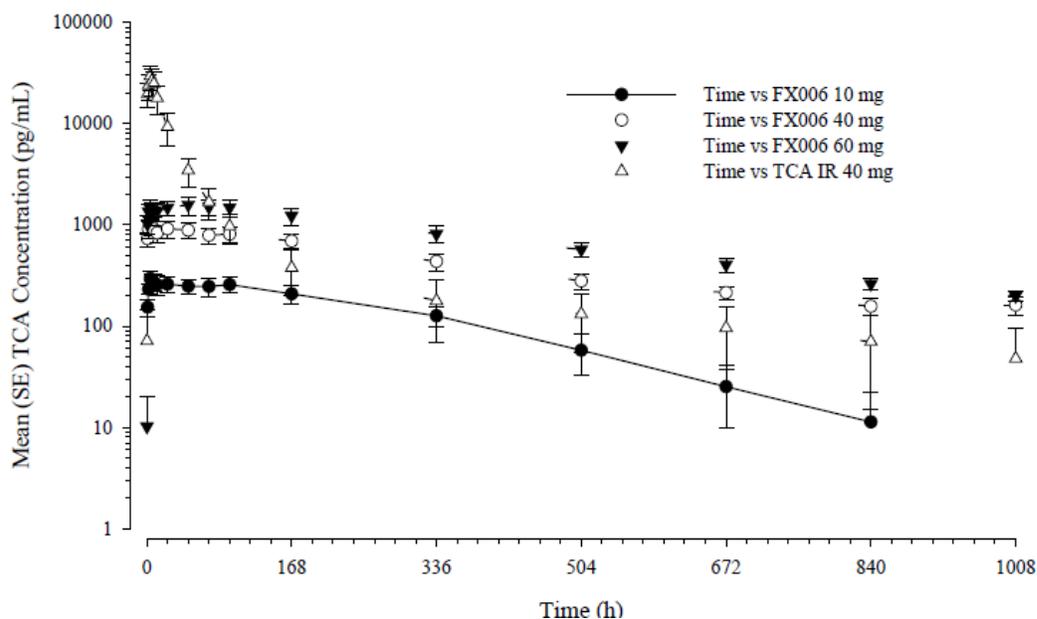
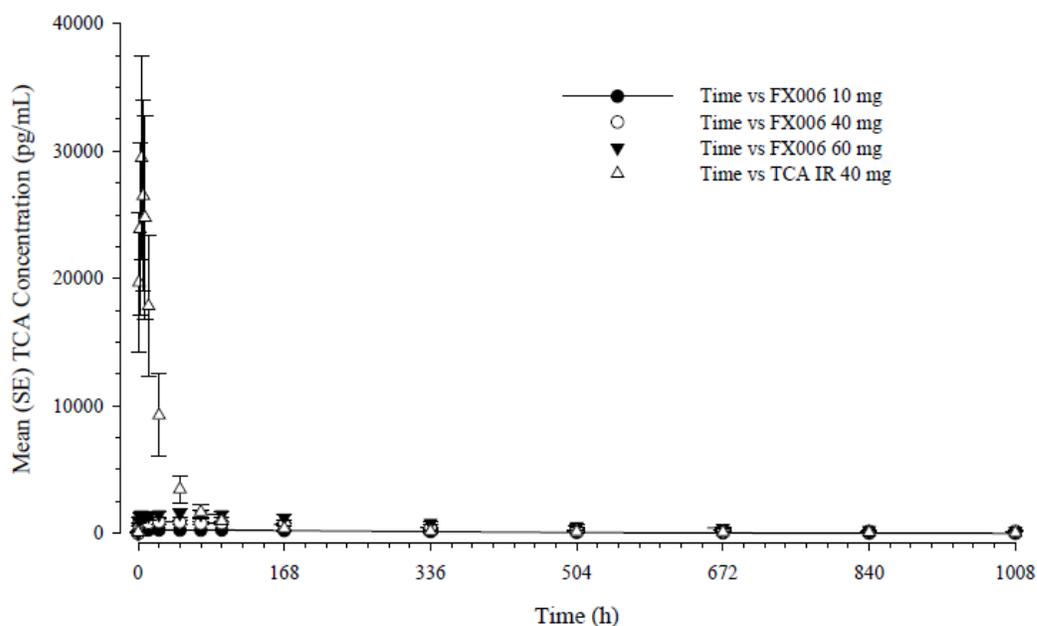
1. A single IA injection of FX006 results in a pattern of cortisol suppression that is dose- and time-dependent.
2. Only slight cortisol suppression was observed with FX006 10 mg that remained consistent over the course of the study and was less than that observed with TCA IR before week 6.
3. Serum cortisol suppression with 40 mg and 60 mg FX006 peaked in the first 24 hours, was greater than that observed with TCA IR at week 2, and gradually returned to near Baseline levels by week 6.
4. A near expected level of cortisol suppression was observed and peaked in the first 24 hours following administration of TCA IR and returned to near Baseline levels earlier than that seen with the 40 and 60 mg doses of FX006.

Although the Sponsor demonstrated decrease and recovery in cortisol levels during the study, change in serum cortisol levels is not used as a primary test to assess HPA axis function, suppression, or its ability to respond to stress. Absolute values of morning cortisol and dynamic testing (ACTH stimulation test) of the HPA axis are the accepted and preferred methods to evaluate the HPA axis if there is concern for adrenal insufficiency (4, 5). Dynamic testing of the HPA axis was not performed in this study. Although the Sponsor collected morning cortisol levels, they did not analyze these values in their assessment of the effect of FX006 on the HPA axis. Given that in the endocrine community, assessment of absolute morning cortisol values has greater utility than change in serum cortisol to assess HPA axis function over time, this medical officer analyzed absolute values of morning cortisol as described in the next section and shown in Table 3.

The Sponsor also calculated geometric mean percent difference (data not shown) from baseline in morning serum cortisol for the different dose groups and the “Cumulative Cortisol Suppression (CCS %)”. The CCS % has been described as a tool to evaluate the potential clinical effects of FX006 relative to other corticosteroid products. The CCS% represents a PK/PD model developed by Meibohm et al. (6) to quantify and predict the cumulative systemic activity after *inhaled* corticosteroid administration. However, the CCS % model has not been validated in clinical studies for any route of corticosteroid administration. Therefore, these data cannot be relied upon and will not further be discussed in this review.

Lastly, the Sponsor states that FX006 results in a slower release of TCA in the systemic circulation suggesting that the microspheres of FX006 resulted in better retention of TCA concentrations at the site of injection given the difference in concentration between TCA IR and 40 mg of FX006 (Figure 2): the profile of TCA IR was characterized by rapid absorption into the systemic circulation and concentrations were markedly higher than those observed for the FX006 treatment groups. Per the Sponsor, the slower release of TCA in FX006 is an important consideration as it allows exposure to TCA to be minimized in the systemic circulation and may reduce untoward systemic effects associated with steroid. *Although the pharmacokinetics might suggest a lesser effect of FX006 on the HPA axis, the effect is not absent (see interpretation of cortisol data below).*

Figure 2. Mean concentration-time profiles of TCA in plasma (linear and linear-log scale)



Source: Sponsor's CSR, page 69/555

Medical Officer analysis of serum cortisol data

This Medical Officer conducted an independent analysis of the submitted Sponsor's data in order to evaluate the effect of FX006 on HPA axis function. For brevity, select serum cortisol levels that provide adequate representation of the pattern of cortisol production over the course of the 6 week study are included in Table 3. Each subject's serum cortisol levels were reviewed independently and as part of the group.

Before interpreting the data in Table 3, the following points are important to understand regarding interpretation of cortisol levels as accepted in the practicing Endocrine community and recommended in the adrenal insufficiency literature.

- Cortisol production follows a diurnal rhythm with the highest serum cortisol levels generally observed between 6AM – 8AM with a steady decline throughout the day and evening and reaching a nadir between 11:30PM and 12:00 midnight (“late night cortisol”). Morning cortisol levels are highly variable, but, not typically below 3 µg/dL and not typically > 25 µg/dL (4, 5). Late night cortisol levels should be < 2 µg/dL.
- A morning serum cortisol level of ≤ 3 µg/dL signifies the possibility of adrenal insufficiency. A morning serum cortisol level of ≥ 19 µg/dL suggests that the patient is adrenally sufficient and does not need any further evaluation for AI. Patients with morning serum cortisol levels of > 3 but < 19 µg/dL are considered ‘indeterminate’. In this setting (and occasionally, when serum cortisol level is < 3 µg/dL, but the diagnosis is still not clear), the need for testing should be based on the pre-test probability of adrenal insufficiency (e.g. baseline symptoms consistent with adrenal insufficiency) (4,5).
- Evening cortisol levels are usually low in subjects with normal HPA axis function and can be < 3 µg/dL. These low levels typically represent a low pulse in cortisol secretion.

Based on the guidelines stated above, this Medical Officer implemented the following *general* strategy to interpret the data in Table 3:

- Serum cortisol levels measured in the morning (AM) or evening (PM), after receipt of study drug on Day 1, were considered indicative of some degree of HPA axis suppression if the respective values were:
 - significantly lower than the Day -1 AM or PM value or the Day 1 pre-dose value

Similarly, to describe the results, the following definitions were used:

- The term “HPA axis suppression” implies study drug effect on the HPA axis causing any level of reduction in cortisol levels.
- The term “HPA axis recovery” refers to diminished study drug effect on the HPA axis as demonstrated by any increase in serum cortisol levels from the lowest post-dose value during the study. Study drug was administered on the morning of Day 1.
- The term “full recovery” implies disappearance of study drug effect on the HPA axis as demonstrated by returning of cortisol levels to baseline values (Day -1 AM and/or PM or Day 1 pre-dose levels).

Table 3. FX-006-2011-002 Serum cortisol levels (µg/dL) by dose group

| Subj ID | Dose | Day -1 AM | Day -1 PM | Day 1 Pre-dose, AM | Day 1 Post-dose 12 h, PM | Day 1 Post-dose 24 h, PM | Day 3 AM | Week 1 AM | Day 14 AM | Week 4 AM | Day 42 AM |
|---------|------|-----------|-----------|--------------------|--------------------------|--------------------------|----------|-----------|-----------|-----------|-----------|
| | | | | | | | | | | | |

| | | | | | | | | | | | |
|--------|-------|------|------|------|------|------|------|------|------|------|------|
| 90-003 | IR | 17.7 | 8.0 | 29.6 | 2.3 | 2.0 | 1.5 | 16.3 | 17.5 | 20.3 | 17.8 |
| 90-006 | IR | 16.8 | 4.6 | 13.1 | 1.9 | 1.8 | 1.1 | 13.8 | 11.6 | 14.4 | 15.9 |
| 91-005 | IR | 20.2 | 9.0 | 20.3 | 1.4 | 1.4 | 1.2 | 16.5 | 19.1 | 27.5 | 15.7 |
| 91-012 | IR | 13.6 | 3.3 | 22.6 | 1.2 | 1.1 | 1.7 | 23.9 | 15.7 | 22.9 | 22.1 |
| 91-017 | IR | 6.9 | 1.6 | 10.2 | 1.1 | 16.3 | 19.3 | 10.8 | 5.3 | 9.3 | 5.1 |
| 90-001 | 10 mg | - | 2.9 | - | 2.8 | 14.6 | 12.2 | 9.7 | - | 16.7 | - |
| 90-010 | 10 mg | 19.7 | 5.7 | 14.8 | 3.7 | 12.8 | 14.8 | 12.8 | 20.0 | 15.1 | 12.1 |
| 91-003 | 10 mg | 17.9 | 8 | 13.6 | 8.7 | 14.2 | 12.1 | 12.5 | 14.6 | 21.7 | 15.8 |
| 91-009 | 10 mg | 17.0 | 7.3 | 24.6 | 15 | 13.8 | 12.7 | 13.2 | 15.6 | 15.4 | 19.1 |
| 91-016 | 10 mg | 9.7 | 5.3 | 13.9 | 3.7 | 7.8 | 15.2 | 12.7 | 13.1 | 14.5 | 9.3 |
| 90-002 | 40 mg | - | 4.2 | 17 | 1.0 | 8.1 | 6.3 | 8.4 | - | 12.4 | - |
| 90-019 | 40 mg | 12.8 | 5.4 | 12.3 | 1.6 | 8.1 | 8.4 | 14.2 | 14 | 15.4 | 14.9 |
| 90-021 | 40 mg | - | 4.4 | 19 | 1.6 | 5.2 | 8.1 | 10.2 | 9.7 | 12.2 | 16.5 |
| 91-002 | 40 mg | 10 | 1.9 | 28.3 | 1.0 | 9.4 | 7.5 | 10.0 | 7.7 | 15.6 | 6.7 |
| 91-008 | 40 mg | 21.8 | 9.6 | 19.7 | 6.0 | 20.1 | 20.8 | 14.1 | 16.5 | 15.6 | 13.6 |
| 91-014 | 40 mg | 15 | 5.4 | 19.5 | 3.1 | 9.7 | 10.3 | 8.4 | 12.2 | 8.5 | 9.7 |
| 91-018 | 40 mg | 13.3 | 3 | 17.1 | 1.3 | 10.3 | 10.0 | 11.5 | 10.3 | 21.6 | 24.1 |
| 90-004 | 60 mg | 17.6 | 5.4 | 19.0 | 2.6 | 10.1 | 1.2 | 10.2 | 15.5 | 15.1 | 21.7 |
| 90-012 | 60 mg | 8.9 | 3.2 | 13.7 | <1.0 | <1.0 | 2.2 | 4.3 | 8.6 | 18.4 | 6.8 |
| 90-018 | 60 mg | 11.6 | 2.3 | 18.6 | <1.0 | 2.5 | 3.5 | 5.7 | 5.9 | 12.3 | 12.9 |
| 91-004 | 60 mg | 18.5 | 20.9 | 19.8 | 1.4 | 1.5 | 1.3 | 2.8 | 6.5 | 22.8 | 15.1 |
| 91-006 | 60 mg | 13.5 | 4.5 | 13.5 | 3.3 | 14 | 14.1 | 13.1 | 15.5 | 19.5 | 15.5 |
| 91-015 | 60 mg | 12.3 | 3.9 | 11.1 | <1.0 | 15.6 | 7.2 | 9.2 | 10.3 | 11.4 | 9.4 |
| 91-020 | 60 mg | 19.3 | 5.5 | 19.5 | - | 4.3 | 8.3 | - | 12.8 | 14.2 | 18.6 |

Source: NDA 208845, Data Tabulation Dataset "ZC"

Study drug administered on Day 1 in the morning

Day 42 = Week 6

AM cortisol levels were drawn between 7-9 AM

PM cortisol levels were drawn between 7-9 PM

Pre-dose, before FX006 administration on Day 1

Post-dose, after FX006 administration on Day 1

Liquid chromatography/tandem mass spectrometry was used for all cortisol measurements

Light blue highlight represents two time points in which HPA axis suppression is most evident

General observations (Table 3 data)

- Notable intra-individual variation is observed in pre-dose cortisol levels as demonstrated by the Day -1 AM vs. Day 1 pre-dose values; this variation can be considered normal.
- Notable inter-individual variation is observed among subjects within the same dose groups in pre- and post-dose cortisol levels; this variation can be considered normal.
- Normal diurnal rhythm in cortisol values was exhibited between Day -1 AM and Day -1, 12 hour post-dose (PM) in all but one participants (91-004) who had Day -1 high evening serum cortisol levels. This subject had normally functioning HPA axis throughout the remainder of the study as demonstrated by lower cortisol values at appropriate times. Four subjects (91-017 (IR), 90-001 (10 mg), and 91-002 (40 mg), and 90-018 (60 mg) had Day -1 PM serum cortisol values of < 3.0 µg/dL. However, in the evening, these low levels can be normal representing the diurnal rhythm of cortisol and

do not represent adrenal insufficiency. Review of adverse event terms reported by these subjects did not show any signs or symptoms of adrenal insufficiency.

Below, for each dose group, general observations regarding the pattern of cortisol fluctuation pre- and post- dose as well as relevant subject data is provided.

TCA IR 40 mg group

- Compared to the Day -1 PM values the Day 1, 12 h post-dose cortisol values (PM) were noticeably lower, indicating some degree of HPA axis suppression from TCA IR administration. This suppression continues as is reflected by the low Day 3 AM cortisol values.
- The HPA axis appears to recover by Week 1 in all subjects.
 - Subj 91-017 has AM serum cortisol levels in the “lower” range of normal throughout the study with the exception of the higher Day 3 serum cortisol increase to 19.3. This subject’s Day 1 24 h post-dose value was also increased at 16.3 suggesting that this patient’s HPA axis rebounded quickly after the TCA IR injection. Upon recovery from acute suppression, the HPA axis can exhibit a hyper-response (personal experience SA), which might explain the higher serum cortisol levels at Day 1 24 h post-dose and Day 3 followed by a return to baseline “lower” AM serum cortisol levels.

FX006 10 mg Group:

- Day 1 12 h post-dose values (PM) reflect mild suppression of the HPA axis.
- Day 3, Week 1, Day 14 and Day 42 (Week 6) show increasing AM cortisol levels that seem to return to baseline, i.e. HPA axis recovery, by Day 14.

FX006 40 mg Group

- Day 1 post-12 hour cortisol values (PM) shows evidence of some degree of HPA axis suppression.
- Cortisol values increase as seen from Day 3 AM onwards: the HPA axis appears to fully recover between Week 4 and Day 42 (Week 6) in the majority of subjects. Recovery is questionable in subject 90-002 because of missing data; and, in subject 91-014 because of AM cortisol levels < 10 at Week 4 and Day 42 compared to AM pre-dose levels of >15 µg/dL.

FX006 60 mg Group

- Day 1 post-12 hour cortisol values show some degree of HPA axis suppression as all of the values are lower than what is seen in the Day -1 AM values and some values are clearly suppressed at less than 1.0 µg/dL.
- Day 3, Week 1 and Day 14 AM serum cortisol levels appear to be increasing in all subjects.
- Week 4 and Day 42 AM cortisol levels similar to Day -1 AM and Day 1 pre-dose levels in all subjects, which suggests full recovery of the HPA axis.

Based on review of the Sponsor's morning cortisol data (Table 3), this Medical Officer agrees with the Sponsor's conclusions that a single IA injection of FX006 resulted in dose- and time-dependent cortisol suppression with maximal cortisol suppression observed within the first 24 hours and HPA axis function recovery by Day 42, i.e. Week 6.

However, the following study limitations complicate the assessment of HPA axis function and do not allow us to provide a definitive conclusion regarding the clinically meaningful HPA axis suppression and risk of overt adrenal insufficiency:

- The Sponsor did not perform clinical assessment for signs and symptoms of adrenal insufficiency of the enrolled subjects at any point throughout the study.
- The Sponsor did not require that any serum cortisol level be drawn fasting nor was there any requirement regarding whether the serum was drawn via venipuncture or through an indwelling catheter. Systemic cortisol levels are pulsatile throughout a 24 h period with many peaks and valleys and are influenced by food intake and stress, i.e. single or multiple venipunctures and multiple other exposures. Thus, to limit variability, endocrine protocols usually mandate that morning serum cortisol levels are drawn under fasting conditions and be drawn in a consistent manner whether it is via venipuncture or an indwelling catheter. How the lack of a standard protocol affected the intra- and inter-individual variation in cortisol levels pre- and post-dosing is not known.

Safety Data

Overall, FX006 was well-tolerated. There were no deaths, serious adverse events or significant adverse events reported in the FX006-2011-002 study, and no patients prematurely discontinued due to an AE during the study.

However, the Sponsor did not include specific assessment for signs and symptoms of adrenal insufficiency in the protocol; thus, the evaluation of occurrence of adrenal insufficiency during the study is complicated. Overall, clinical signs of adrenal insufficiency are non-specific and include fatigue, dizziness, nausea, headache, etc. Thus, this Medical Officer reviewed the AE terms for all 24 subjects and concluded that the pattern of the reported AE terms was not consistent with signs and symptoms of adrenal insufficiency. Two subjects in 10 mg group had symptoms suspicious of AI: moderate nausea/vomiting (subject 91-009) and severe lethargy (subject 90-010); however, neither subject's cortisol values suggest significant HPA axis suppression or adrenal insufficiency throughout the study.

There were no clinically relevant changes in mean or median vital sign parameters throughout the study in any of the dose groups. Also, laboratory shifts were reviewed and were not clinically relevant with regard to HPA axis suppression or adrenal insufficiency.

References:

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- 2) **Reid DM, Eastmond C, Rennie JA** 1986 Hypothalamic-pituitary-adrenal axis suppression after repeated intra-articular steroid injections. *Ann Rheum Dis* 45:87.
- 3) **Broersen LHA, Pereira AM, Jorgensen JOL, Dekkers OM** 2015 Adrenal insufficiency in corticosteroid use: Systematic review and meta-analysis.
- 4) **Grinspoon SK, Biller BMK** 1994 Clinical Review 62: Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab* 79:923-931.
- 5) **Nieman L** 2003 Dynamic evaluation of adrenal hypofunction. *J Endocrinol Invest* 26 (Suppl. to no. 7): 74-82, 2003.
- 6) **Meibohm B, Hochlaus G, Mollmann H, Barth J, Wagner M, Krieg M, Stockmann R, Derendorf B** 1999 A pharmacokinetic/pharmacodynamic approach to predict the cumulative cortisol suppression of inhaled corticosteroids. *J Pharmacokinet Biopharm* 27:127-47

Appendix 1. Eligibility Criteria, Study FX006-2011-002

Inclusion Criteria:

1. Written consent to participate in the study
2. Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
3. Male or female ≥ 35 years of age
4. Diagnosis of unilateral or bilateral OA of the knee for at least 6 months prior to Screening with confirmation of OA according to American College of Rheumatology (ACR) Criteria for Classification of Idiopathic OA of the Knee (clinical and radiological) based on an X-ray performed within 6 months prior to Screening or during the Screening period
5. Index knee pain on most days (>15) over the last month
6. Body mass index (BMI) ≤ 40 kg/m²
7. Morning serum cortisol result within normal range at Screening
8. Ambulatory and in good general health
9. Willingness to abstain from use of the following during the study:
 - Oral, inhaled, or intranasal corticosteroids
 - IA corticosteroids in any joint
 - IA viscosupplementation (hyaluronic acid) in the index knee

Exclusion Criteria (next page):

Disease-related criteria

1. History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis or amyloidosis
2. History of arthritides due to crystals (e.g., gout, pseudogout)
3. History of infection in the index joint
4. Clinical signs and symptoms of active knee infection or crystal disease of the index knee
5. Presence of surgical hardware or other foreign body in the index knee
6. Unstable joint (such as a torn anterior cruciate ligament)

Previous or concomitant treatment-related criteria

7. IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening
8. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
9. Oral, inhaled or intranasal corticosteroids (investigational or marketed) within 1 month of Screening
10. Any other IA investigational drug/biologic within 6 months of Screening
11. Prior arthroscopic or open surgery of the index knee within 12 months of Screening
12. Planned/anticipated surgery of the index knee during the study period

Patient-related criteria

13. Known hypersensitivity to any form of triamcinolone
14. Known hypersensitivity to ethyl chloride
15. History of or active malignancy, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ within 5 years
16. Known active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex
17. History of any infection requiring intravenous antibiotics within 4 weeks of Screening, history of infection requiring oral antibiotics within 2 weeks of Screening, history of chronic infection, or a history of osteomyelitis

18. Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses
19. Screening or Baseline 12-lead ECG demonstrating QTc >450 msec in male patients and >470 msec in female patients or any clinically significant ECG abnormality as judged by the Principal Investigator
20. Insulin-dependent diabetes
21. History of or active Cushing's syndrome
22. Any other clinically significant acute or chronic medical conditions (*e.g.*, uncontrolled diabetes) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study
23. Positive drug or alcohol screen
 - NOTE: a drug screen that is positive for opioids for a patient admittedly taking prescription opioids for pain is allowed.
24. Skin breakdown at the knee where the injection would take place
25. Women who are pregnant or nursing
26. Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using a highly effective method of contraception (oral, injected or implanted hormonal methods of contraception; intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or male sterilization (vasectomy)).
27. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
28. Has received a live or live attenuated vaccine within 6 months of Screening
29. Use of any other investigational drug or device within 30 days of Screening or an investigational biologic within 60 days of Screening

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/s/

SMITA B ABRAHAM
08/14/2017

MARINA ZEMSKOVA
08/14/2017

JEAN-MARC P GUETTIER
08/14/2017

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Patrick Archdeacon, Medical Officer
THROUGH: Lisa Yanoff, Medical Team Leader, DMEP/ODEII
TO: File
SUBJECT: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
consult for NDA 208,845
PRODUCT: FX006 (proposed tradename Zilretta; triamcinolone ER injection)
SPONSOR: Flexion Therapeutics
DATE: August 9, 2017

BACKGROUND

Flexion Therapeutics submitted an original NDA to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on December 8, 2016 for FX006 (proposed tradename Zilretta; triamcinolone ER injection). FX006 is a synthetic corticosteroid with the proposed indication of management osteoarthritis (OA) pain of (b) (4) by intra-articular injection. FX006 was designed as an extended-release (ER) formulation of triamcinolone acetonide (TCA): it contains TCA formulated in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% weight/weight (w/w). FX006 is provided as a sterile powder and is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride, sodium carboxymethylcellulose, and polysorbate-80 to form a suspension prior to intra-articular administration; each vial contains a nominal 40 mg of triamcinolone acetonide in 160 mg of microspheres.

Published literature suggests currently marketed corticosteroids, including some other formulations of triamcinolone, used for intra-articular injections have observable effects on glycemic control in patients with type 2 diabetes mellitus (T2D) as well as on the hypothalamic-pituitary-adrenal (HPA) axis.¹ DAAAP consulted the Division of Metabolism and Endocrine Products (DMEP) to review and comment on the pharmacodynamics portion of the study designs and results of two studies included in the Ziltretta NDA submission and comment on the proposed labeling in Section 12.2 of the Prescribing Information. DMEP is providing two separate consults: this memo is dedicated to the effect of FX006 on glycemic control in T2D patients; another memo dedicated to the effect of FX006 on the HPA axis will also be issued from DMEP.

The NDA package included data from study FX006-2015-010, a study intended to elucidate the effects of FX006 on glycemic control in patients with type 2 diabetes mellitus (T2D). In addition to review of the data from and the final clinical study report for FX006-2015-010, materials reviewed included the FX006-2015-010 statistical analysis plan, draft labeling for Zilretta proposed by Flexion Therapeutics, approved labeling for Kenalog-40 (a marketed formulation of TCA injectable used as the active comparator in FX006-2015-010), and the published literature included in the references for this memo.

EXECUTIVE SUMMARY

Study FX006-2015-010 demonstrates a statistically significant difference exists between the impact of FX006 and TCA IR on certain metrics of glycemic control in patients with type 2 diabetes. However, the sponsor provides no justification for a margin for any of these metrics to support a conclusion that the differences observed are clinically meaningful. Moreover, even if FDA agreed that the FX006-2015-010 data are sufficient to establish that use of FX006 is less likely than TCA IR to cause adverse events related to hyperglycemia, (b) (4)

[REDACTED]

DMEP REVIEW

The sponsor reports that its other studies conducted during the development of FX-006-2015-010 show that injection of FX006 resulted in lower plasma concentrations of TCA but higher synovial concentrations compared to injections of TCA immediate release formulations, suggesting that use of FX006 may mitigate systemic adverse reactions observed with use of TCA IR intra-articular injections. FX006-2015-010 was a double-blind, randomized, active controlled trial conduct to test this hypothesis by comparing the effects on FX006 and Kenalog-40 (TCA suspension) on blood glucose in patients with T2D and OA of the knee.

The primary objective of FX006-2015-010 was the assessment of the effects of a single intra-articular injection of 40 mg of FX006 on blood glucose levels in patients with T2D relative to 40 mg of TCA IR. Inclusion/Exclusion criteria specified that patients must be ≥ 40 years of age, have HbA1c $\geq 6.5\%$ and $<9\%$, stable on 1 or 2 oral antihyperglycemic agents, not be using an injectable antihyperglycemic agents, demonstrate adequate blood glucose (BG) data collection during the pre-treatment phase, and have no recent history of corticosteroid use.

The protocol called for 36 patients to be randomized to 1 of 2 treatment groups:

- 40 mg FX006, administered as single 5 ml IA injection
- 40 mg TCA IR (Kenalog-40), administered as single 1 ml IA injection

After screening and enrollment, blood glucose concentrations were measured using a Dexcom Z4 Platinum Professional continuous glucose monitor (CGM) device (set to blinded mode) for 1 week prior to intra-articular injection of study drug and for 2 weeks after the injection. A final safety visit was scheduled at 6 weeks post-injection.

FX-006-2015-010 was a blinded study with regards to the patient and the assessor. However, due to differences in appearance and preparation between FX006 and TCA IR, the study was not blinded with regards to the pharmacist preparing the study drug or to the health care provider who administered the injection. The injection contents were not visible to the patient.

Schedule of Assessments

Screening (Day -21 to Day -7): IC, Inclusion/Exclusion review, MH, OA and DM history, prior treatment and medications, knee assessment, knee x-ray, PE, ECG, VS, labs

Pre-treatment (Day -7): CGM sensor placed

Baseline (Day 1): Inclusion/Exclusion review, MH update, prior treatment and medications, knee assessment, PE, VS, labs, CGM sensor replaced, CGM data uploaded and reviewed, randomization, treatment administration, AE data collected, concomitant medications collected

Day 8: Knee assessment, VS, CGM sensor replaced, CGM data uploaded, AE data collected, concomitant medications collected

Day 15: Knee assessment, VS, CGM sensor removed, CGM data uploaded, AE data collected, concomitant medications collected

Week 6/EoS: Knee assessment, PE, VS, labs, AE data collected, concomitant medications collected

Pharmacodynamic Assessment

Patients monitored blood glucose levels using the Dexcom Z4 Platinum Professional CGM sensor from Day -7 through Day 15. Calibration of the CGM was done using a Bayer Contour Standard Glucose Measuring meter. CGM sensors were replaced on Day 1 and Day 8. CGM data from Day -7 through baseline were uploaded and reviewed to confirm eligibility prior to randomization.

Statistical Analysis Plan

Primary objective: assessment of effects of single IA injection of 40 mg FX006 on blood glucose levels in patients with T2D, relative to 40 mg of TCA IR

Adjustment for covariates: The primary model and secondary continuous endpoints will include baseline (72-hour) average blood glucose as a baseline covariate. Study site will also be included in the MMRM as a categorical covariate.

Primary endpoint: change in average blood glucose from baseline (Hour -72 to Hour 1) to Day 1-3 (Hour 1 to Hour 72) post IA injection for 40 mg FX006 relative to 40 mg TCA IR, tested at a two-sided α 0.05 level (interim analysis set to 0.001, final analysis set to 0.049). Analysis done using the full analysis set (all subjects randomized) using ANCOVA with fixed effects.

Secondary endpoints: 1) AUC for average BG; 2) percent of time hourly average BG in various BG categories for each day from Day 1 to Day 15; 3) glycemic variability (calculated as CV of the hourly averages), 4) time to maximum BG levels, 5) cumulative distribution of BG, 6) maximum BG levels, All secondary endpoints are also tested at a two-sided alpha 0.05 level without adjustments for multiple endpoints (therefore descriptive only, since no specified hierarchy).

Missing data: All data available will be used. Denominator for calculating means will be total number of non-missing glucose values in time period. No missing data will be imputed.

Randomization: Minimization randomization used according to baseline average blood glucose categories (mean BG \leq 157.32 mg/dl; 157.32 mg/dl < mean BG < 177.44 mg/dl; mean BG \geq 177.44 mg/dl)

Reviewer comment on SAP: the SAP was amended prior to database lock to specify that patients in the FAS will be analyzed "as treated" (rather than as randomized). This was done because it was discovered that three patients received the incorrect treatment (that is, they were randomized to one treatment but received the other). While the decision to change the analysis strategy was done before database lock, this approach conflicts with intent-to-treat principles.

Reviewer comment on FX-2015-010 design: FX006-2015-010 was intended as a comparative safety study to test the hypothesis that use of FX006 would have a more favorable effect on average blood glucose over a relatively short duration of time than TCA IR in a population of patients with T2D. We note that the study primarily evaluates PD endpoints, i.e., blood glucose levels, rather than HbA1c, the usual validated surrogate used in glycemic control trials designed to demonstrate efficacy of an anti-diabetic therapy, or hard clinical outcomes associated with poor glycemic control. While the sponsor argues that the effects of TCA IR on glycemic control may have clinical consequences (ranging from relatively mild adverse reactions such as polyuria or blurry vision to potentially more serious reactions such as diabetic ketoacidosis) the study design did not allow for a meaningful assessment of these outcomes. Finally, the study relies on glucose measurements obtained from the use of a CGM device, in particular the Dexcom Z4 Platinum Professional. In general, due to issues with device performance, DMEP does not recommend using data collected with CGM devices to support regulatory decision making, although there are some newer devices with improved accuracy that have this potential (the Dexcon Z4 is not one of these newer devices). Despite these design limitations, FX-2015-010

represents a reasonable effort to address an important clinical question. Please see Recommendations below for additional discussion.

FX006-2015-010 Results

An error in updating the investigational product inventory list resulted in three patients receiving the incorrect treatment assigned after randomization (see Table 1). Patient 023-1010 and patient 030-1012 were randomized to TCA IR but received FX006; patient 054-1003 was randomized to 40 mg FX006, but received TCA IR. The error was detected prior to database lock and the SAP was amended at that time to conduct the primary analysis according to actual treatment received rather than randomized treatment. Results presented in this review follow this convention.

Table 1: Actual Treatment received after randomization

| | Actual Treatment | |
|-------------------|------------------|--------|
| | FX006 | TCA IR |
| Planned Treatment | | |
| FX006 | 16 | 1 |
| TCA IR | 2 | 14 |
| Total | 18 | 15 |

Derived from FX006-2015-010 datasets

Table 2: Subject Disposition

| | FX006 (n=18) | TCA IR (n=15) |
|---|-----------------|------------------|
| Completed through EoS | 17 | 15 |
| Completed through Day 15 data collection | 18 | 15 |
| Included in Full Analysis Set | 18 | 15 |
| Protocol non-compliance after injection (unwilling to return for EoS visit) | 1 | 0 |

Derived from FX006-2015-010 datasets

The error in treatment assignment after randomization led to a small imbalance in the distribution of baseline glucose levels across treatment arms. While the protocol used a stratification strategy to minimize differences in this category, the incorrect delivery of treatment intervention to the three affected patients resulted caused this imbalance.

Table 3: Study Demographics

| | FX006 (n=18) | TCA IR (n=15) |
|--|-----------------|------------------|
| Sex | | |
| Male | 12 | 8 |
| Female | 6 | 7 |
| Race | | |
| White | 15 | 9 |
| Black | 3 | 5 |
| Asian | 0 | 1 |
| Baseline Avg Blood Glucose Category | | |
| ≤ 157.32 mg/dl | 10 | 10 |
| 157.33 – 177.43 mg/dl | 5 | 1 |
| ≥ 177.44 mg/dl | 3 | 4 |

Derived from FX006-2015-010 datasets

Impact on Glycemic Control

Table 4 shows the percent time in range, i.e. categorical cutoffs for glucose values. Note that the category 70 – 180 mg/dL is the target range. Values below are considered hypoglycemia, and values above are considered hyperglycemia. In Figure 1, the average glucose tracing for each subject is shown over time, with time zero being when the drug was injected. There appears to be a slight increase in glucose values in the FX006 group with a more noticeable increase in the TCA IR group. In both groups, glucose values appear to revert to baseline after 72 hours.

The sponsor’s primary analysis (Figure 2), following the amended SAP to compare actual treatment groups, demonstrated a statistically smaller Least Squares Means change in average daily blood glucose from baseline to Day 1-3 for FX006 compared to TCA IR with a p-value of 0.0452. The secondary analyses presented from FX-2015-010 qualitatively support a conclusion

that FX006 had less effect than TCA IR on glycemic control in the days after intra-articular injection (see Table 4, Figure 1, and Figure 2).

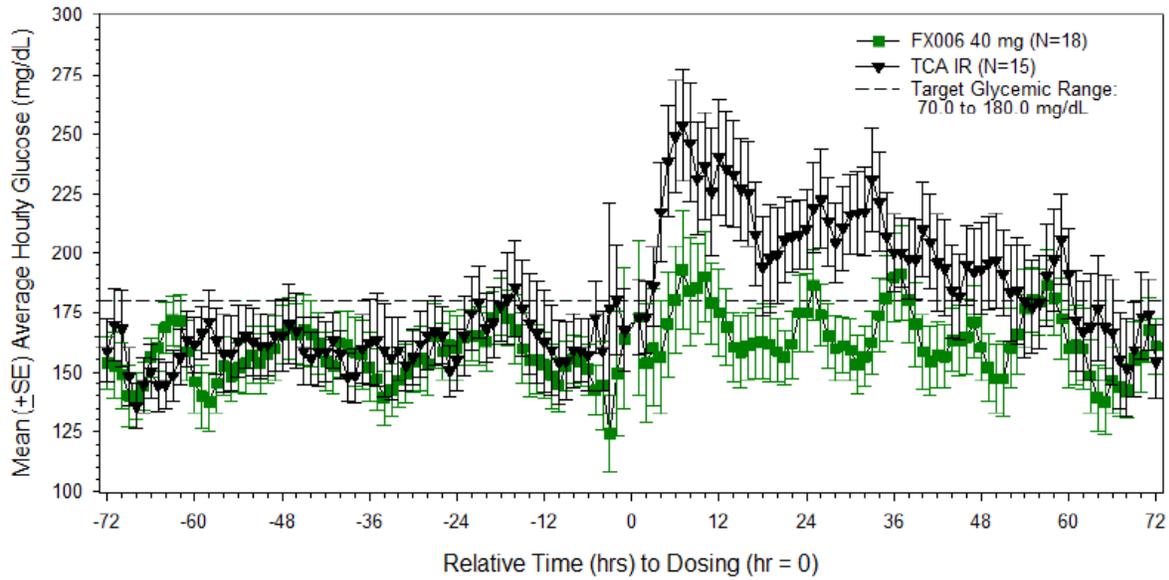
Table 4: Percent of Time in Range for Average Daily Blood Glucose by Category (FAS)

| Time point | Parameter/Statistic | FX006 40 mg (N=18) | TCA IR 40 mg (N=15) |
|------------|------------------------------------|-----------------------|------------------------|
| Day 1 | N1 ¹ | 18 | 15 |
| | Blood glucose (mg/dL) category - % | | |
| | <70.0 | 1.4 | 0.3 |
| | 70.0-180.0 | 64.1 | 41.9 |
| | 180.1-250.0 | 22.0 | 25.3 |
| | 250.1-350.0 | 11.1 | 25.8 |
| Day 2 | N1 ¹ | 18 | 15 |
| | Blood glucose (mg/dL) category - % | | |
| | <70.0 | 1.0 | 0.3 |
| | 70.0-180.0 | 64.7 | 44.6 |
| | 180.1-250.0 | 23.7 | 29.0 |
| | 250.1-350.0 | 8.6 | 23.9 |
| Day 1-2 | N1 ¹ | 18 | 15 |
| | Blood glucose (mg/dL) category - % | | |
| | <70.0 | 1.2 | 0.3 |
| | 70.0-180.0 | 64.1 | 42.7 |
| | 180.1-250.0 | 23.0 | 27.4 |
| | 250.1-350.0 | 9.9 | 25.2 |
| | >350.0 | 1.7 | 4.4 |

¹ N1 is the number of evaluable patients. The percents for each category are based on the number of evaluable patients.

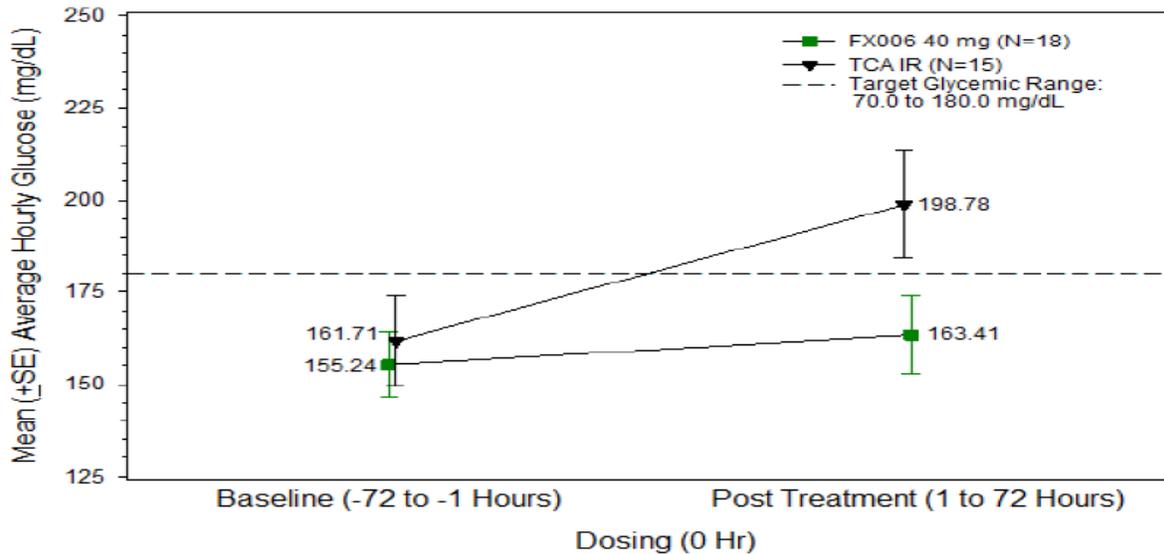
Source: FX-2015-010 CSR, p.62

Figure 1: Mean Average Blood Glucose by Hour (-72 Hours to 72 Hours)



Source: FX-2015-010 CSR, p.58

Figure 2: Mean Change from Baseline for Average Blood Glucose (-72 Hours to 72 Hours)



Source: FX-2015-010 CSR, p.59

Reviewer Comment: FX006-2015-010 was designed as a comparative PD trial to test the hypothesis that use of FX006 would have less impact on glycemic control over a 72 hour period than TCA IR in a population of patients with T2D. The formal hypothesis testing returned a p-value less than 0.05, supporting a conclusion that FX006 is associated with a smaller change in average blood glucose levels in the 72 hours after IA injection than TCA IR. The strength and usefulness of this conclusion is somewhat mitigated by 1) the use of an amended SAP that

analyzed the data by actual treatment received rather than by randomization assignment; 2) the reliance on CGM to collect values for blood glucose, despite the limitations of this technology for accurately measuring blood glucose; and 3) most importantly, the lack of justified, clinically significant margin: while the data support a statistically significant difference in the impact of FX006 and TCA IR on glycemic control, the clinical significance of this numeric difference is unclear. While FX006 and TCA IR appear to have different impacts on glycemic control, the observed blood glucose values before and after injection for the 18 subjects that received FX006 suggest that FX006 does have an impact on glycemic control (the mean change in average blood glucose in the FX006 group for the 72 hour period after injection is 8.2 mg/dL (standard deviation 26); the least squares mean change was 15 mg/dL (standard error 7.0)). Overall, the study results support a conclusion that FX006 is associated with a smaller change in average blood glucose levels than TCA IR, but do not convincingly show that use of FX006 in patients with type 2 diabetes will not have adverse effect on glycemic control nor that use of FX006 in such patients will lead to meaningfully clinically different outcomes than use of TCA IR. It is unlikely that perturbations in mean glucose in the range observed in the study for the 72 hour duration will have notable clinical impact over the long term; however, some subjects in the TCA IR group had temporary blood glucose increases up to 275 mg/dL which is considered concerning hyperglycemia has the potential to result in symptoms and clinical decompensation. While an imbalance in adverse events was not observed in the study (see Table 5 below) the study was relatively small and in theory preventing blood glucose from reaching as high as 275 mg/dL would be advantageous. We recommend that DAAAP consider how often a single patient might receive treatment with this product to better understand the clinical significance of glucose changes.

Adverse Events

With regards to safety outcomes, few adverse events were reported in this short-duration 33 subject trial. The single reported event of hyperglycemia occurred in the FX006 study arm. No serious adverse events of any kind were reported in FX006-2015-010 (see Table 5).

Table 5: Adverse Events Observed in FX006-2015-010

| | FX006 (n=18) | TCA IR (n=15) |
|------------------------|-----------------|------------------|
| Adverse Events (Total) | 3 | 2 |
| <i>Back pain</i> | 0 | 1 |
| <i>Ecchymosis</i> | 0 | 1 |
| <i>Hyperglycemia</i> | 1 | 0 |

| | | |
|------------------------|---|---|
| Hypertension | 1 | 0 |
| Vomiting | 1 | 0 |
| Serious Adverse Events | 0 | 0 |

Derived from FX-2015-010 datasets

Reviewer comment: The adverse event data collected in FX006-2015-010 illustrate the limits of the trial. The data do not convincingly demonstrate that the statistically significant differences observed on blood glucose levels correlate with clinically meaningful differences.

Sponsor-proposed language in Zilretta Draft Labeling Section 12.2

The sponsor has proposed the following language regarding the findings of FX006-2015-010 for inclusion in section 12.2 (Pharmacodynamics) of the Zilretta labeling:

Corticosteroids may increase blood glucose concentrations. (b) (4)
 (b) (4)

Reviewer comment: (b) (4)
 (b) (4)
 (b) (4) FX006-2015-010 was designed to evaluate whether FX006 would have less effect than TCA IR on blood glucose over the 72 hours post dosing. Overall, FX006-2015-010 supports a finding that FX006 has less impact on glycemic control than TCA IR, though flaws in study design and deficiencies in study conduct limit the robustness of this conclusion. (b) (4)

(b) (4) The available PD data from the study suggest that FX006 does impact glycemic control and the adverse event data captured one non-serious event of hyperglycemia in the 18 patients receiving FX006. (b) (4)

Conclusions and recommendations

(b) (4)
 (b) (4)
 (b) (4)

FX006-2015-010 provides data demonstrating that FX006 has less impact on glycemic control than does TCA IR, the data (as analyzed) do not demonstrate that the impact of FX006 on glycemic control is not clinically significant.

The results of FX006-2015-010 are intriguing and possibly of interest of healthcare providers and patients. Certainly the results appear appropriate for communication in published peer-review literature. (b) (4)

If DAAAP believes that the findings of FX006-2015-010 would provide useful information of health care providers and patients, I recommend adding a concise quantitative description of the observed effect of FX006 on glycemic control (e.g., “Corticosteroids may increase blood glucose concentrations. In a study where 18 patients with osteoarthritis knee pain and controlled type 2 diabetes mellitus received a (b) (4) intra-articular (b) (4) of FX006, the change from baseline in average blood glucose over the 72 hours after injection as measured by a continuous glucose monitoring device was 8.2 mg/dL (95% confidence interval 0.1, 29.2).” DMEP does not typically rely on data from continuous glucose monitoring devices for labeling of products intended to improve glycemic control, as concerns exist about the accuracy of the measurements. For that reason, I recommend also consulting with CDRH to determine whether the performance of the Dexcom Z4 Platinum Professional CGM sensor is adequate to support the statement I’ve proposed.

This information could potentially be added to Section 12.2 Pharmacodynamics to describe a clinical effect related to AR or toxicity. Alternatively, DAAAP may wish to consider whether corticosteroids should have a class warning in Section 5 regarding hyperglycemia. If class labeling is pursued, it may be reasonable to add the quantitative description of the effect of FX006 observed in FX-2015-010 to its warning.

ⁱ Habib GS. “Systemic effects of intra-articular corticosteroids” Clin Rheumatol (2009) 38: 749-56.

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/s/

PATRICK ARCHDEACON
08/10/2017

LISA B YANOFF
08/10/2017

JEAN-MARC P GUETTIER
08/11/2017

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: July 26, 2017

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 208845

Product Name and Strength: Zilretta (triamcinolone acetonide extended-release injectable suspension), 32 mg per vial

Product Type: Single ingredient combination product

Rx or OTC: Rx

Applicant/Sponsor Name: Flexion Therapeutics, Inc.

Submission Date: December 8, 2016, March 3, 2017, and July 21, 2017

OSE RCM #: 2017-103

DMEPA Primary Reviewer: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review provides our evaluation of the proposed labels and labeling for Zilretta (triamcinolone acetonide extended-release injectable suspension) from a medication error perspective. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review as part of their evaluation of the 505(b)(2) NDA submission for Zilretta.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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 |
| Human Factors Study | C-N/A |
| ISMP Newsletters | D-N/A |
| FDA Adverse Event Reporting System (FAERS)* | E-N/A |
| Other | F-N/A |
| Labels and Labeling | G |

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and to identify other areas that can be improved.

The proposed product is supplied as a kit in a carton containing one vial of Zilretta microsphere powder, one vial of diluent (5 mL), and one sterile vial adapter. Preparation of Zilretta requires the health care professional to reconstitute the microsphere powder with the supplied diluent, by using the vial adapter, and re-suspend the suspension prior to administration. We previously determined that the Applicant does not need to conduct Human Factors studies because healthcare professionals are the intended users of the product and because the vial adapter is an approved device used with other marketed products.

Container Labels and Carton Labeling

Our review of the diluent and Zilretta container labels determined that there is inadequate differentiation. We are aware of post-marketing errors of other powder products packaged

with a diluent where the diluent alone was administered to the patient.^a Thus, we recommend the Applicant increase the prominence of the word, “Diluent” on the diluent container label by use of different colors, boxing, or some other means to provide adequate differentiation from the Zilretta powder container label. Additionally, we recommend the Applicant relocate the statement, “Do not administer directly” from the side panel of the diluent container label to the principal display panel and use bold font to increase prominence and minimize the risk of healthcare professionals administering the diluent alone to patients.

We note the carton labeling includes the statement, “Must be reconstituted,” which is inconsistent with the container label statement on the Zilretta powder vial, (b) (4). We are aware of post-marketing errors involving other powder products packaged with a diluent where the powder was reconstituted with a diluent other than the supplied diluent.^b In order to minimize the risk for these errors, we recommend the Applicant revise this statement on the container label and carton labeling to read, “Must be reconstituted with the supplied diluent” for clarity and consistency. Furthermore, we recommend the Applicant use different colors, boxing, or some other means to increase prominence of this statement.

We note the statement, “Resuspend completely and only with diluent provided (5 mL)” is located on the side panel of the carton labeling. We recommend the Applicant replace “Resuspend” with “Reconstitute” for consistency with the other statements on the container label and carton labeling.

We note that the storage information for Zilretta differs from the listed drug, Kenalog-40. Zilretta is refrigerated (36°-46°F; 2°-8°C). If refrigeration is unavailable, Zilretta can be stored in the sealed, unopened kit at temperatures not exceeding 77°F (25°C) for up to six weeks. Conversely, Kenalog-40 is not refrigerated and is stored at controlled room temperature, 20°–25°C (68°–77°F). We are concerned that the difference in storage information between Zilretta and Kenalog-40 may lead to wrong storage errors due to confirmation bias from previous experience with Kenalog-40. Thus, we recommend the Applicant add the statement, (b) (4) and increase the prominence of the storage information on the container label and carton labeling by use of bold font.

The Zilretta microsphere powder and diluent are supplied in clear glass vials (b) (4). (b) (4)

^a Institute for Safe Medication Practices. Safety Briefs: Diluent vial looks like drug vial. ISMP Med Saf Alert Acute Care. 2012;17(17):2-3.

^b Institute for Safe Medication Practices. Administering just the diluent or one of two vaccine components leaves patients unprotected. ISMP Med Saf Alert Acute Care. 2012;19(10):1-4.

The carton labeling does not include the contents supplied in the carton. Thus, we recommend the Applicant revise the carton labeling to include the contents (for example, one vial of Zilretta microsphere powder, one vial of diluent (5 mL) for Zilretta, and one sterile vial adapter).

We identified undefined abbreviations (for example, IV and ID) on the carton labeling. Thus, we recommend the Applicant replace these undefined abbreviations with their full meaning.

We note the established name is not included in parenthesis. Thus, we recommend Applicant revise the presentation of the established name on the container labels and carton labeling so that it is included in parenthesis.

We identified that the package type term “Single-use vial” is present on the diluent container label, which is inconsistent with the package type term on the Zilretta powder container label “Single dose vial.” [REDACTED] (b) (4)

[REDACTED] We notified the Office of Pharmaceutical Quality (OPQ) reviewer of this inconsistency by email and we defer to OPQ to determine the correct package type term for this product and convey this to the Applicant.

We contacted OPQ to verify the correct dosage form for Zilretta and recommend the Applicant ensure the OPQ-approved dosage form is presented on all labels and labeling.

Prescribing Information (PI)

We note that the Dosage and Administration section in the Highlights of Prescribing Information does not include the statement, “See [REDACTED] (b) (4) for instructions on reconstitution of Zilretta with the supplied diluent.” We are concerned that healthcare professionals may overlook important preparation instructions if they refer to the Highlights of Prescribing Information only. Thus, we recommend adding this statement to the Highlights of Prescribing Information to alert healthcare providers of the preparation instructions in the Full PI and to minimize the risk for these errors.

We note that the Dosage and Administration section in the Highlights of Prescribing Information does not include the non-interchangeability statement that is located in Section [REDACTED] (b) (4) of the full PI. Thus, we recommend adding this statement to the Highlights of Prescribing Information to alert healthcare providers of this important information and to minimize the risk for substitution errors.

We note that Section 2 Dosage and Administration in the full PI refers to the Instructions for Use (IFU), but does not include the IFU. We recommend the full IFU be included in Section 2 Dosage and Administration of the full PI to minimize the risk for preparation and administration errors.

Instructions for Use (IFU)

We note that the figures in the IFU are not labeled. Thus, we recommend the Applicant label the figures in the IFU for clarity (for example, figure 1), and reference them in text as appropriate.

We note that specific information within the “Important Information” section is difficult to locate in the paragraph format. Thus, we recommend the Applicant improve readability of this section by use of a bulleted list.

We recommend the Applicant use bold font for the statement, “ZILRETTA must be prepared using the diluent supplied in the kit” and relocate it to be the first bullet under the “IMPORTANT INFORMATION” section to increase prominence of this important information and to minimize the risk of preparation and administration errors.

We note the figure under Step 1 of the vial being tapped does not depict a padded surface under the vial. Thus, we recommend revising this figure to include a padded surface to improve clarity.

We recommend the Applicant revise the heading, “Attach vial adapter” to read, “Attach vial adapter to Zilretta powder vial” and add “ZILRETTA powder” prior to “Vial” in the figure caption “Vial with adapter in place” for clarity and to minimize the risk of healthcare providers attaching the vial adapter to the diluent vial.

We recommend relocating the statement, “Note: Avoid shaking the vial to minimize foam” to under the heading “Mix Diluent and Powder” to increase prominence of this important information.

According to the Office of Pharmaceutical Quality (OPQ), healthcare professions should use a 21-gauge needle to ensure that a consistent dose is delivered. Thus, we recommend revising the “Not Supplied” section of the IFU to include (b) (4) the 21-gauge needle.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

4.1 RECOMMENDATIONS FOR THE DIVISION

We revised the *Dosage and Administration* section of the Highlights of Prescribing Information and Full Prescribing Information and provided a detailed summary below for review and consideration by DAAAP.

A. General Comment

1. (b) (4)
We defer to the Office of Pharmaceutical Quality (OPQ) to make the final determination of the (b) (4) package type term for this product. Ensure that the OPQ-determined package type is consistent throughout labels and labeling and is conveyed to the Applicant.
2. We note the Applicant lists (b) (4) as the dosage form in their submission for proprietary name review, but the PI, container label, and carton labeling present the dosage form as “extended release injectable

suspension.” Thus, ensure the correct OPQ-determined dosage form is presented on all labels and labeling.

B. Highlights of Prescribing Information

1. We recommend adding the statement, “See (b) (4) for instructions on reconstitution of Zilretta with the supplied diluent.” to the Dosage and Administration section to alert healthcare providers of the preparation instructions and to minimize the risk for errors.
2. We recommend adding the statement, “ZILRETTA is not interchangeable with other formulations of injectable triamcinolone acetonide. (b) (4)

(b) (4)

C. Full Prescribing Information

1. We recommend replacing the information in Section 2.2 Preparation and Administration of Intra-Articular Suspension with the full IFU to minimize the risk for preparation and administration errors. Ensure that the recommendations for the IFU in section 4.2 below are implemented in the IFU in the PI.

4.2 RECOMMENDATIONS FOR FLEXION THERAPEUTICS, INC.

We recommend the Applicant implement the following prior to approval of this NDA:

A. Zilretta Container Label (including Professional Sample)

1. Revise the statement, (b) (4) to read, “Must be reconstituted with the supplied diluent” for clarity and consistency. Furthermore, we recommend you use different colors, boxing, or some other means to increase prominence of this statement. We are aware of post-marketing errors involving other powder products packaged with a diluent where the powder was reconstituted with a diluent other than the supplied diluent.^c
2. Add the statement, (b) (4) (b) (4) for clarity. Use bold font for this statement to increase the prominence of the storage information and minimize the risk of storage errors.
3. (b) (4)
4. Revise the presentation of the established name so that the established name is included in parenthesis.

B. Diluent Container Label (including Professional Sample)

^c Institute for Safe Medication Practices. Administering just the diluent or one of two vaccine components leaves patients unprotected. ISMP Med Saf Alert Acute Care. 2012;19(10):1-4.

1. Increase the prominence of the word “DILUENT” by use of different colors, boxing, or some other means to provide adequate differentiation from the Zilretta powder container label. We are aware of post-marketing errors of other powder products packaged with a diluent where the diluent alone was administered to the patient.^d To accommodate this change, decrease the size of the “5 mL” statement. Additionally, use bold font for the statement, “Do not administer directly” and relocate the statement from the side panel to the principal display panel to increase prominence and minimize the risk for errors. To accommodate this change, relocate the statement, “Sterile single-use vial” from the principal display panel to the side panel.
 2. See A.3
- C. Carton Labeling (including Professional Sample)
1. Revise the statement, “Must be reconstituted” to read, “Must be reconstituted with the supplied diluent” for clarity and consistency. Furthermore, we recommend you use different colors, boxing, or some other means to increase prominence of this statement. We are aware of post-marketing errors involving other powder products packaged with a diluent where the powder was reconstituted with a generic diluent instead of the supplied diluent.^e
 2. Revise the statement, “(b) (4) at 2-8°C (36-46°F). (b) (4) Do not freeze. Store vial in carton” to read, “(b) (4) at 2-8°C (36-46°F). Do not freeze. Store vials in carton” for clarity. Use bold font for this statement to increase the prominence of the storage information and minimize the risk of storage errors.
 3. Include the contents of the carton on the principal display panel. For example:
“This carton contains:
-1 vial of Zilretta microsphere powder
-1 vial of diluent (5 mL) for Zilretta
-1 sterile vial adapter”
To accommodate this addition, consider relocating the manufacturer logo from the principal display panel to the side or back panel.
 4. Replace the abbreviations IV and ID on the side panel with their full, intended meaning.^f
 5. See A.4
- D. Instructions for Use (IFU)
1. Label the figures in the IFU for clarity (for example, figure 1), and reference them in text as appropriate.

^d Institute for Safe Medication Practices. Safety Briefs: Diluent vial looks like drug vial. ISMP Med Saf Alert Acute Care. 2012;17(17):2-3.

^e Institute for Safe Medication Practices. Administering just the diluent or one of two vaccine components leaves patients unprotected. ISMP Med Saf Alert Acute Care. 2012;19(10):1-4.

^fGuidance 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>

2. To improve the readability of the “Important Information” section, consider presenting information in a bulleted list.
3. Use bold font for the statement, “ZILRETTA must be prepared using the diluent supplied in the kit” and relocate the statement as the first bullet immediately below the heading “IMPORTANT INFORMATION” to increase prominence of this important information and to minimize the risk of preparation and administration errors.
4. The figure under Step 1 of the vial being tapped does not depict a padded surface under the vial. Thus, we recommend revising this figure to include a padded surface to improve clarity.
5. Revise the heading, “Attach vial adapter” to read, “Attach vial adapter to Zilretta powder vial” and add “ZILRETTA powder” prior to “Vial” in the figure caption “Vial with adapter in place” for clarity and to minimize the risk of healthcare providers attaching the vial adapter to the diluent vial.
6. Relocate the statement, “Note: Avoid shaking the vial to minimize foam” to under the heading “Mix Diluent and Powder” to increase prominence of this important information.
7. According to the Office of Pharmaceutical Quality (OPQ), a 21-gauge needle should be used to ensure consistent dose delivery. Thus, revise the “Not Supplied” section to include (b) (4) the 21-gauge needle (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zilretta (triamcinolone acetonide extended-release injectable suspension) that Flexion Therapeutics, Inc. submitted on March 3, 2017, and the listed drug (LD).

| Table 2. Relevant Product Information for Zilretta and the Listed Drug | | |
|---|---|--|
| Product Name | Zilretta | Kenalog-40 |
| Initial Approval Date | Not Applicable | February 1, 1965 |
| Active Ingredient | triamcinolone acetonide | triamcinolone acetonide |
| Indication | management of osteoarthritis pain of (b) (4) | as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis, or osteoarthritis. |
| Route of Administration | intra-articular | intra-articular |
| Dosage Form | injectable suspension | injection |
| Strength | 32 mg | 40 mg |
| Dose and Frequency | 32 mg once | 2.5 mg to 5 mg for smaller joints and from 5 mg to 15 mg for larger joints, depending on the specific disease entity being treated. For adults, doses up to 10 mg for smaller areas and up to 40 mg for larger areas have usually been sufficient. Single injections into several joints, up to a total of 80 mg, have been given. |
| How Supplied/ Container Closure | 5 mL (b) (4) vial (b) (4) 32 mg of triamcinolone acetonide (b) (4) | 1 mL, 5 mL, 10 mL vials |

| | | |
|----------------|--|--|
| | <p>(b) (4) supplied as a sterile, white to off white powder in a cerium glass (clear) (b) (4) vial with a rubber stopper and an aluminum seal with a gray plastic cap.</p> <p>Diluent: 5 mL (b) (4) vial supplied as a sterile, clear liquid solution of 0.9% w/w sodium chloride (normal saline) containing 0.5% w/w sodium carboxymethylcellulose, and 0.1% w/w polysorbate-80 in a glass vial with a rubber stopper, aluminum seal and white plastic cap.</p> | |
| Storage | <p>The ZILRETTA (b) (4) kit should be refrigerated (36°-46°F; 2°-8°C).</p> <p>If refrigeration is unavailable, the ZILRETTA (b) (4) kit can be stored in the sealed, unopened kit at temperatures not exceeding 77°F (25°C) for up to six weeks. Do not expose the ZILRETTA (b) (4) kit to temperatures above 77°F (25°C).</p> | <p>Store at controlled room temperature, 20–25C (68°–77°F), avoid freezing and protect from light. Do not refrigerate.</p> |

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 3, 2017, we searched the L:drive and AIMS using the term, Zilretta, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified did not identify previous reviews relevant to the current label and labeling review.

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁸ along with postmarket medication error data, we reviewed the following Zilretta (triamcinolone acetonide extended-release injectable suspension) labels and labeling submitted by Flexion Therapeutics, Inc. on December 8, 2016 and July 21, 2017.

- Container Label
- Diluent Label
- Carton Labeling
- Professional Sample Container Label
- Professional Sample Diluent Label
- Professional Sample Carton Labeling
- Instructions for Use

G.2 Label and Labeling Images

Container Label



7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

⁸ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILLIE C BRAHMBHATT
07/26/2017

OTTO L TOWNSEND
07/26/2017

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: June 9, 2017

To: Kimberly Compton, Program Coordinator
CDER/OND/ODEII/DAAAP

From: LCDR Keith Marin, CDRH/ODE/DAGRID/GHDB

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for NDA 208845, ICC1700027

| | |
|-----------------------------|--|
| Applicant | Flexion Therapeutics, Inc |
| Indication for Use | management of osteoarthritis pain of the (b) (4) |
| Drug / Biologic Constituent | triamcinolone acetonide injection ("Zilretta") |
| Device Constituent | Vial adapter |

Recommendation: Based on information reviewed NDA 208845, the sponsor has provided sufficient information for the vial adapter. All interactive review questions have been satisfactorily addressed. As a result, CDRH/ODE recommends approval for the BLA for this combination product.

| Digital Signature Concurrence Table | |
|-------------------------------------|---|
| Reviewer | Keith G. Marin -S Digitally signed by Keith G. Marin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=0011250397 Date: 2017.06.19 15:46:32 -04'00' |
| Branch Chief | Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2017.07.06 14:12:18 -04'00' |

I. Purpose / Background

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding a review request for NDA 208845. The device

constituent of this combination product consists of a vial adapter designed for use with commercial off-the-shelf Luer-Lock syringes, which are not included in packaging with the product. The vial adapter and 20mm vial are assembled together by the user (i.e. healthcare provider) at the time of administration. Triamcinolone acetonide injection ("Zilretta") is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. indicated for management of osteoarthritis pain of the (b) (4)

The original consult request from CDER indicates that, "As soon as possible, preferably to be discussed with the team at the Filing Mtg on 1/18/17, but not later than the Filing date of 2/3/17, we request initial review and concurrence on the Fileability of this combination drug-device product (i.e., everything needed to complete a review of the submission is provided in the application) and, if the NDA is filed, review of device aspects of the product. If all of the needed information to review the application is not provided, we request a delineation of additional items needed ASAP."

The device presentation that is being evaluated within this review is a vial adapter. The syringe is not part of the review as the sponsor has stated that the vial adapter is intended to be used with an off the shelf syringe. Device performance will be the focus of this review. Device/drug compatibility will be deferred to CDER.

CDR Alan Stevens provided information shared with the firm at the Pre-NDA meeting (under IND 111325 in May 2016.

II. Administrative

Documents Reviewed:

| Cross-Referenced 510(k) # | Letter of Authorization Included in NDA / BLA | |
|---------------------------|---|----|
| | YES | NO |
| (b) (4) | X | |

Reviewer's Note: The sponsor has provided reference to (b) (4) and provided a letter of authorization to review information.

| Document Title | Document Number | Date –Version | Location |
|--------------------------------|---|---------------|---------------------------------------|
| User Requirement Specification | Container Closure System [FX006 (triamcinolone acetonide extended release powder for suspension for injection), 40 mg | 12/08/2016 | GSR Sequence 0000 / Section 3.2.P.7.3 |
| | | | |

CDRH Review Team:

| Team Member | Role | Deficiencies |
|-----------------------------------|--------------------------------|--------------|
| LCDR Keith Marin (CDRH/ODE/GHDB)} | Lead Reviewer – Nurse Reviewer | 0 |

III. Device Description and Performance Requirements

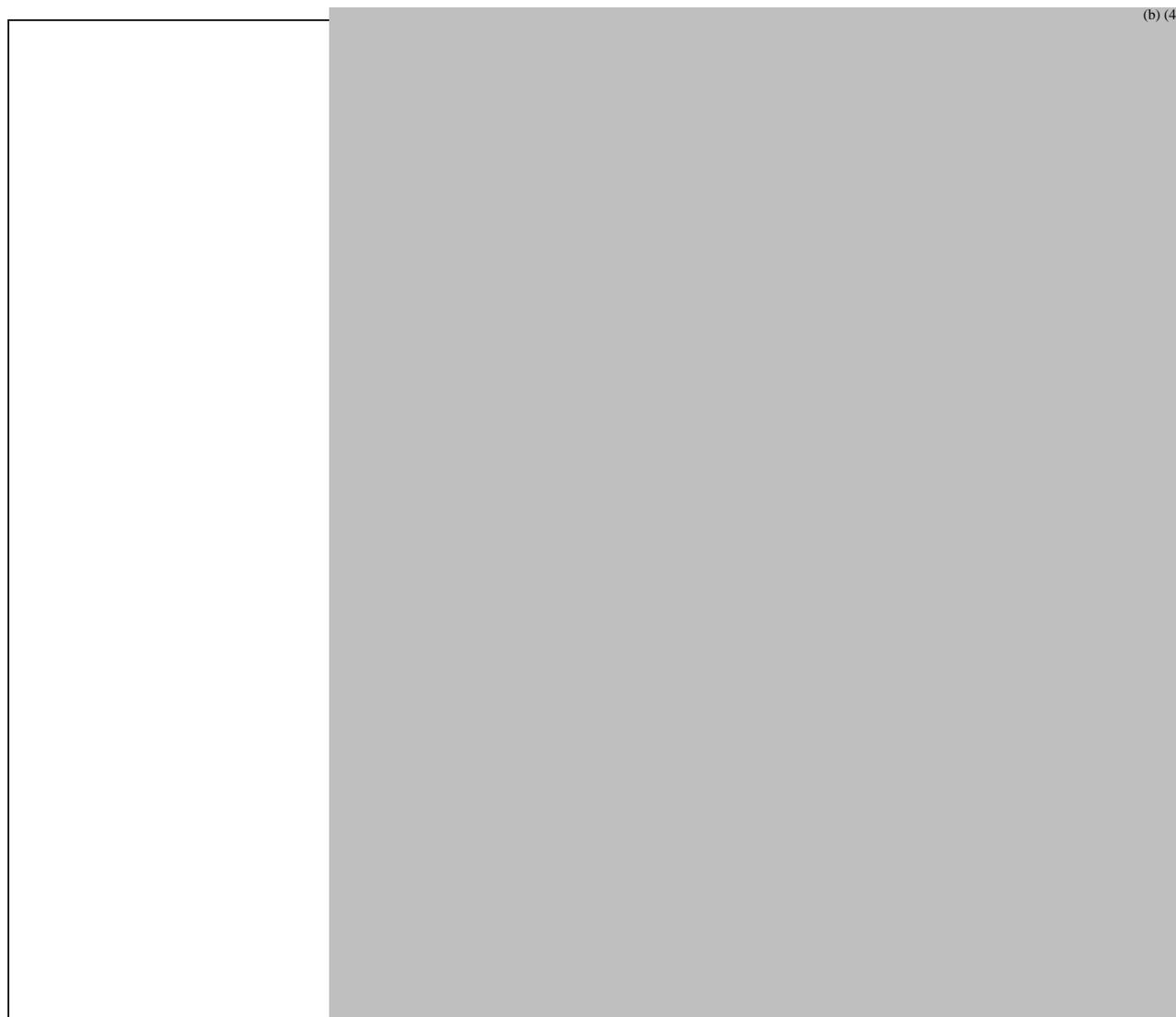
| | |
|---|---|
| Indications for Use | |
| Zilretta (Triamcinolone acetonide extended release injectable suspension) | ZILRETTA is an extended release synthetic corticosteroid indicated as an intra-articular injection for the management of osteoarthritis pain of (b) (4) |

(b) (4)



| Device Characteristic | Description / Specification |
|-----------------------|-----------------------------|
|-----------------------|-----------------------------|

| | |
|--|---|
| Vial Adapter body | (b) (4) |
| Blister package | |
| Lid | |
| Vial Adapter Specifications | Height is 25.7mm, width is 30.4mm. Diameter of opening of vial adapter is 23.6mm. Connection is 6% female luer taper that is ISO 594 compliant. |
| Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use) | Professional use for transfer of drug to syringe for intra-arterial injection (b) (4). |
| Storage conditions and expiry | (b) (4) month shelf life testing conducted, ZILRETTA single-use kit should be refrigerated (36°-46°F; 2°-8°C). (b) (4) |
| Preparation and administration (describe all that are applicable) <ul style="list-style-type: none"> • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc. | (b) (4) |



IV. Design Control Review

A. Design Control Documentation Check

| Design Control Requirement* | Signed/Dated Document Present | | Submission Location |
|---|-------------------------------|----|---|
| | Yes | No | |
| Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer | X | | 3.2.P.5.1, Quality Information Amdendment 4/28/2017 |
| Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file. | X | | Quality Information Amdendment 4/28/2017 |
| Risk Analysis supplied in the NDA / BLA by the Combination Product Developer | X | | QA-SOP-021, Risk Management for Medical Devices and Combination Products, Document Number: DH-011 |

| | | | |
|-----------------|---|--|-------|
| Validation Data | X | | 3.2.R |
|-----------------|---|--|-------|

B. Design Verification and Validation Review

| Standard / Guidance | | Conforms | | |
|---------------------|---|----------|----|-----|
| | | Yes | No | N/A |
| Connections | ISO 594-1: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: General Specifications | X | | |
| | ISO 594-2: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: Lock Fittings | X | | |

| Component | Requirement | Summary | Results | Deviations | Reference Documents |
|--|---|---|---------------------------------|------------------------------------|---|
| Finished Goods (All packaged components) | (b) (4) month shelf life | Real-time aging for the vials. Accelerated aging for vial adapter, IFU, and packaging | PASS | IFU and packaging aging is pending | Appendix 10 Appendix 11 Refer to Module 3.2.P.8.1 Stability Summary and Conclusion (Drug Product) Refer to Module 3.2.P.8.1 Stability Summary and Conclusion (Diluent) |
| Finished Goods (All packaged components) | Transportation | Perform simulated distribution testing and confirm functionality. | To be completed prior to launch | Preparing protocols | Appendix 12 Appendix 13 |
| Packaging | Packaging contains drug vial, diluent vial, vial adapter, and IFU | Dimensional check followed by assembly with actual product during process validation. | To be completed prior to launch | Packaging execution is pending | Pending |
| Packaging Label | Compliant with 21 CFR 201 and USP <1> risk control elements. | Inspect printed carton to confirm elements are included and described appropriately. | PASS | None | Refer to Module 1.14.1.1 Draft Carton and Container Labels |
| IFU | Compliant with 21 CFR 201 and USP <1> risk control elements. | Inspect IFU to confirm elements are included and described appropriately. | PASS | None | Refer to Module 1.14.1.3 Instructions for Use |

| Component | Requirement | Summary | Results | Deviations | Reference Documents |
|--------------|-------------------------------|---|---------|------------|--|
| Vial Adapter | Biocompatibility | Execute 10993-1 for the vial adapter. | PASS | None | Appendix 3 Appendix 4 Appendix 5 Appendix 6 Appendix 7 Appendix 8 Appendix 9 |
| Vial Adapter | Sterility | (b) (4) | PASS | None | Appendix 14 |
| Vial Adapter | Physical Compatibility | Vial adapter fits on the 20mm drug vial, establishing fluid path without leaks. | PASS | None | Appendix 15 |
| Vial Adapter | Physical Compatibility | Measure the penetration force of installing the vial adapter on the drug vial | PASS | None | Appendix 15 |
| Vial Adapter | Chemical Compatibility | Risk assessment confirms chemical compatibility of the resuspended drug product with the vial adapter | PASS | None | Refer to Module 4.2.3.7.6 Leachable Report RPT60848.00 |
| Vial Adapter | (b) (4) Syringe compatibility | Vial adapter has ISO 594-2 compatible female connector | PASS | None | Appendix 1 |
| Vial Adapter | Ambidextrous use | Vial adapter is symmetrical | PASS | None | Appendix 2 |

Design Verification Review

| Essential Performance | Specification | Verification Test Results |
|-----------------------|---------------|---------------------------|
|-----------------------|---------------|---------------------------|

| Requirement | | PASS | FAIL |
|------------------------|---|------|------|
| Physical compatibility | Vial adapter fits on the 20mm drug vial, establishing fluid path without leaks. | X | |
| Chemical compatibility | Vial adapter is compatible with the resuspended drug product | X | |
| Syringe compatibility | Vial adapter has ISO 594-2 compatible female connector | X | |
| Ergonomics | Vial adapter is symmetrical for right hand/left hand usage | X | |

Table 6: 20mm Vial Adapter Performance Testing Summary

| Performance Test | Acceptance Criteria | Sample Size | Test Results | | Pass / Fail |
|---|---------------------|-------------|------------------------------|----------------------------------|-------------|
| | | | Time 0 Report #3188-R | 5-year Acc. Aging Report #3188-R | |
| Total penetration force test | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |
| Product removal from blister force test | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |
| Detachment force | (b) (4) | 35 | Met acceptance criteria | Met acceptance criteria | Pass |
| Air leakage test | (b) (4) | 29 | No bubble formation observed | No bubble formation observed | Pass |
| Spike tip ductility | (b) (4) | 29 | No spike damage observed | No spike damage observed | Pass |
| Functionality test | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |

Table 7: 20mm Vial Adapter Sterile Barrier Testing Summary

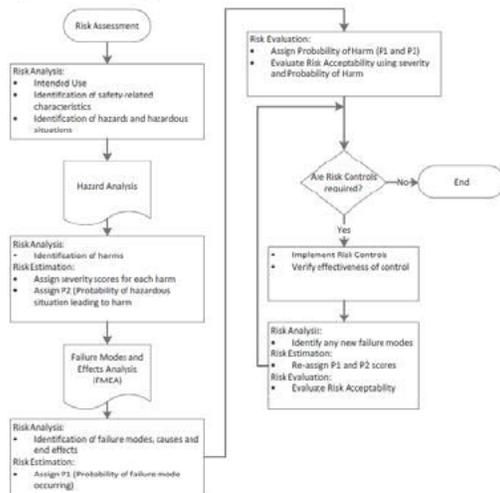
| Performance Test | Acceptance Criteria | Sample Size | Test Results | | Pass / Fail |
|----------------------|---------------------|-------------|------------------------------|----------------------------------|-------------|
| | | | Time 0 Report #3188-R | 5-year Acc. Aging Report #3188-R | |
| Visual inspection | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |
| Peel test | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |
| Bubble test | (b) (4) | 29 | No bubble formation observed | No bubble formation observed | Pass |
| Dye penetration test | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |
| Seal strength | (b) (4) | 29 | Met acceptance criteria | Met acceptance criteria | Pass |

Reviewer's Note: In response to our request for functional testing, the sponsor has provided a summary of the testing. Complete test reports can be found in Appendix 10 in the April 28, 2017 IR response. As the vial adapter is ISO compliant, compatibility with a syringe is not necessary. I find the testing to be acceptable and have no further questions.

Design Validation Review

| Risk Analysis Attributes | Yes | No | N/A |
|--|-----|----|-----|
| Risk analysis conducted on the combination product | X | | |

Figure 5: Risk Management Process



Flexion determined the required activities for design validation by applying a risk-based approach. Flexion has determined that, based on the outputs of the risk management process for the product and demonstrated functionality using (b) (4) materials, the FX006 System can be considered safe and effective for its intended use.

Flexion executed a separate risk analysis for use-related errors when using the FX006 System. The results of this analysis identified no high risks; therefore, the only risks identified were classified as either low or medium. Most of the medium risks were tied to the harm of infection due to improper aseptic procedures or contamination. The remaining medium risks are associated major infections caused by misuse of the vial adapter. These risks were determined to be no different than what would be expected in any other use of the original 510(k) cleared vial adapter system. The sponsor has provided a visual and functional inspection plan to validate function of the device.

Sterilization: Vial adapters (b) (4)

Table 4: Material Testing Requirements

| Test / Attribute | Test Method / Reference | Specification |
|-----------------------------|---------------------------------|-------------------|
| Bacterial Endotoxin | USP <5>, JP <4.01>, EP <2.6.14> | (b) (4) EU/Device |
| Sterility Dose Confirmation | | (b) (4) |

Reviewer’s Note: The sponsor has provided sterilization testing and provided a summary table in Table 4. As the sterility of the vial adapter would have been evaluated in the 510k that is referenced, I do not have any further concerns.

Risk Analysis

Flexion has performed a series of risk analyses on the vial adapter following our internal procedures for risk management as discussed in (b) (4) Risk Management for Medical Devices and Combination Products. Prior to performing the formal risk assessment, a review of the historical complaints as monitored by the FDA’s Manufacturer and Users Facility Device Experience Database (MAUDE) was performed with “20mm vial adapter” in the brand name field. This database highlighted that this

commercially available vial adapter had limited complaints, with only two reports identified over the last 10 years. From this evaluation, no evidence was identified to support correlation between the incident and the devices. Other sources of information used to inform the risk assessments were literature searches (PubMed), clinical trial data bases, and current standard of care assessment. Additionally, a review of the usage of the vial adapter in FX006 clinical studies showed no history of clinical site complaints in over 500 clinical usages during development.

Table 3: User FMEA Severity Totals

| Risk Level | Count | Severity of Harm Level | Count | Hazard ID's |
|------------|-------|------------------------|-------|--|
| High | 0 | N/A | 0 | N/A |
| Medium | 29 | 5 (Catastrophic) | 0 | N/A |
| | | 4 (Critical) | 29 | F9,F10,F11,F16,F17, F20,F24, F33,F34,F35,F36,F37,F39,F42, F47,F54,F55,F65,F66,F70,F72, F74,F83,F89,F94,F97,F101, F109, F111 |
| Low | 81 | 4 (Critical) | 0 | N/A |
| | | 3 (Serious) | 9 | F2,F13,F15,F21,F22,F25,F59, F99,F107 |
| | | 2 (Minor) | 37 | F1,F8,F12,F19,F23,F38,F43, F44,F50,F51,F52,F53,F57,F60, F61,F62,F64,F67,F69,F71,F73, F75,F77,F78,F79,F80,F82,F84, F86,F91,F95,F100,F102,F104, F106,F108,F110 |
| | | 1 (Negligible) | 35 | F4,F5,F6,F7,F14,F18,F26,F27, F48,F28,F29,F30,F31,F32,F40, F41,F45,F46,F49,F56,F58,F63, F68,F76,F81,F85,F87,F88,F90, F92,F93,F96,F98,F103,F105 |

- F9: Opened package is dropped, causing component contamination resulting from inadequate package design (difficult to grasp)
- F10: Gross contamination of components due to preparation in unclean environment resulting from unclear preparations instructions
- F11: Gross contamination of components due to preparation in unclean environment resulting from omission of step
- F16: Gross component contamination resulting from unclear preparations instructions
- F17: Gross component contamination resulting from omission of step
- F20: Glass breakage resulting from too much force
- F24: Glass breakage resulting from not using padded surface
- F33: Stopper is touched after being cleaned resulting from improper aseptic technique used
- F34: Stopper is cleaned and vial is put aside for extended duration resulting from improper aseptic technique used
- F35: Stopper is not cleaned with alcohol wipe resulting from improper aseptic technique used
- F36: Stopper is not cleaned with alcohol wipe resulting from alcohol wipes used are not adequate
- F37: Vial adapter is removed from blister early and contaminated resulting from improper aseptic technique used
- F39: Vial adapter is dropped and becomes contaminated resulting from inadequate material design (unable to grasp)
- F42: Vial adapter lidding from packaging is not completely removed; vial adapter is not accessible resulting from operator error
- F47: Vial adapter does not snap into place securely - product becomes contaminated resulting from inadequate material design
- F54: Needle not attached correctly - product is contaminated resulting from inadequate material design
- F55: A previously used needle is reused and Diluent becomes contaminated resulting from inadequate instructions
- F65: Sterile surface of vial adapter becomes contaminated resulting from inadequate instructions
- F66: Vial adapter and vial are dropped leading to contaminated components resulting from inadequate material design (unable to grasp)

- F70: Syringe and needle are dropped leading to contaminated components resulting from inadequate material design (unable to grasp)
- F72: Syringe is overtightened into vial adapter causing separation - system becomes contaminated resulting from inadequate instructions
- F74: Syringe or vial adapter and vial are dropped leading to contaminated components resulting from inadequate material design (unable to grasp)
- F83: Syringe attached to vial adapter and vial is dropped leading to contaminated components resulting from inadequate material design (unable to grasp)
- F89: Syringe is dropped leading to contaminated components resulting from inadequate material design (unable to grasp)
- F94: Syringe is dropped leading to contaminated components resulting from inadequate material design (unable to grasp)
- F97: Same needle as diluent withdrawal is used - contaminated component used resulting from inadequate instructions
- F101: Needle becomes contaminated due to being dropped resulting from inadequate material design (unable to grasp)
- F109: Injection site is not cared for resulting from omission of step
- F111: Components are reused resulting from inadequate instructions and lead to spread of infectious disease

The risks of these 29 specific hazards detailed above, as well as the 81 hazards categorized as Low Risk, occurring were reduced as low as possible through instructions for use, and expected adherence to use of standard proper aseptic technique during the preparation and administration of intra-articular injections. All available mitigation steps have been taken, including product labeling and detailed instructions for use. Although product labeling and instructions for use are not expected to reduce the probability of a particular hazard occurring, they are still a mitigation strategy.

Reviewer's Note: *The sponsor has listed 29 medium risk hazards that would potentially cause harm to the patient. I do not see any issues with the hazards identified and most (if not all) can be addressed by appropriate instructions for use. I have no further questions.*

Biocompatibility: A biological risk assessment of the vial adapter was performed in accordance with ISO 10993-1:2003 and documented through supplier specifications and testing, which includes assessment of cytotoxicity, hemolysis, intracutaneous, pyrogenicity, sensitization, and systemic toxicity (refer to Table 5). According to a worst case approach, any device that includes the same materials and share the same production process (or less) can be under the scope of the biocompatible report of such device.

(b) (4) vial adapter 20mm is composed of

(b) (4)

The biocompatibility

summary report is available in Appendix 3.

Table 5: Biocompatibility Testing for (b) (4) 30 G needle after 2 cycles of (b) (4)

| Test Performed | Test Method | Result | Reference Document |
|---------------------------------------|--------------|---------------|--------------------|
| Maximization Sensitization | ISO 10993-10 | Pass | Appendix 4 |
| ASTM Hemolysis | ISO 10993-4 | Pass | Appendix 5 |
| Intracutaneous | ISO 10993-10 | Pass | Appendix 6 |
| Systemic Toxicity | ISO 10993-11 | Pass | Appendix 7 |
| Cytotoxicity | ISO 10993-5 | Pass | Appendix 8 |
| USP Rabbit Pyrogen, Material Mediated | ISO 10993-11 | Non pyrogenic | Appendix 9 |

(b) (4)

Reviewer's Note: *The sponsor has provided biocompatibility testing and provided a summary table in Table 5. Based on review of the appendix 4-9, the testing results meet the stated acceptance criteria. As the biocompatibility of the vial adapter would have been evaluated in the 510k that is referenced, I do not have any further concerns.*

Table 3: Visual and Functional Inspections of Vial Adapter 20mm

| Class | AQI (b) (4) | Description of Defect |
|-----------------------|----------------|---|
| Critical ^a | | Any mislabeled shipping case or intermediate carton. Illegible lot number on individual device label. Incorrect lot number on individual device label. Missing blister pack seal. Incomplete blister pack seal (seal margin less than 50% complete). Incorrect construction material. Incorrect expiration date. |
| Major A ^b | | Broken spike. Visible cracks in the device fluid pathway. Missing lot number on individual device label. Critical dimensions out of tolerance (see product drawing). Visible loose foreign particulate matter in the fluid pathway (b) (4) mm ² . Female Luer does not conform to standard. Fluid Pathway occluded. |
| Major B ^c | | Missing or illegible lot number (intermediate box and shipping case). Intermediate box dirty or wet. Spike burr or flash, firmly attached (b) (4) mm. |
| Minor ^d | | Visible cracks in the device body. Lot number text blurred or smeared on carton or case, but readable on device label. Significant color variance of labeling within lot. (b) (4) Visible embedded particulate matter on the device (4) mm ² Loose extraneous construction material inside package. Damaged blister pack. Incorrect number of units in the intermediate or shipping cartons. Loose foreign matter inside blister pack (b) (4) mm ² |

^a A defect that is likely to result in a hazardous or unsafe condition for the individual using the product or a defect that is a major regulatory concern.

^b A defect that is likely to result in the partial or complete failure of a product to function in its intended manner.

^c A defect that would materially reduce the usability of the device for its intended purpose.

^d A defect that is not likely to reduce the usability of the product for its intended purpose, but which may generate some customer dissatisfaction. It is a departure from established standards (may affect appearance) having little effect on the use or operation of the unit.

Shelf Life Testing: Performance testing to verify package integrity and functionality for vial adapter 20mm FLL (b) (4) has been performed by the manufacturer or (b) (4) (NLT (b) (4) and shipping simulation over the labeled expiry date (b) (4) according to the protocol outlined in Appendix 10. A summary of the data is summarized in Table 6 and the detailed report is available in Appendix 11. Sterile barrier packaging testing to support the 20mm vial adapter has also been performed by the manufacturer for the labeled expiry date of the device and is summarized in Table 7.

Reviewer's Note: Functional testing is shown above in memo that demonstrates the device can function at the end of the shelf life. The information provided is acceptable.

C. Labeling

| | |
|--------------------|---------|
| Vial Adapter Label | (b) (4) |
| Drug Vial Labeling | |

D. Design Transfer Activities – Release Specifications

The following release specifications are included for the device constituent within Quality Information Amendment 4/28/2017 (Sequence 0013(14)).

| Attribute | Specification | Test Method |
|------------------|-------------------------------|-------------------------|
| Liquid Leakage | Device does not leak | ISO 594-1 |
| Air Leakage | Device does not leak | ISO 594-1 |
| Stress cracking | Device does not crack at luer | ISO 594-1 and ISO 594-2 |

Table 2: Device Verification Testing following ISO 594-1:1986 and ISO 594-2:1998

| ISO 594-1 | ISO 594-2 |
|------------------|--------------------------|
| Gauging | Liquid Leakage |
| Liquid Leakage | Air Leakage |
| Air Leakage | Separation Force |
| Separation Force | Unscrewing Torque |
| Stress Cracking | Ease of Assembly |
| | Resistance to Overriding |
| | Stress Cracking |

Flexion reviewed the results for compliance with ISO standard 80369-7:2016 and verified that the vial adapter meets the revised standard for Luer connections. (b) (4)

Reviewer's Note: The sponsor has provided verification testing to validate that at release the device meets the essential performance characteristics. I find the proposed testing according to ISO 594-1 and ISO 594-2 to be appropriate and acceptable and have no further questions.

V. Information Request- Sent June 9, 2017

1. We are unable to locate the risk analysis for the vial adapter. Please provide risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.
2. Provide the LOA for (b) (4).

Reviewer's Note: In the June 12, 2017 response, the sponsor has provided the LOA. They have also provided the location and details of the risk analysis. I have no further questions.

VI. Information Requests – Sent April 3, 2017

You have provided summary verification testing in section 3.2.P.7.3. However, we are unable to locate the complete testing. Please provide the complete test reports (or specific location) for the following:

3. Device description that includes the materials, colorants, dimensions, proof of device compatibility with the off the shelf syringes since you will not be including your own syringe)
4. Specific design specifications (you have not explicitly stated what your specifications are for the vial adapter) along with your lot release specifications for the device constituent
5. Biocompatibility testing for the vial adapter (have a brief summary, but no complete testing or a summary report of the ISO 10993-1 testing conducted)
6. Testing that evaluates the device function at the end of shelf life for the vial adapter
7. Shipping studies (according to ASTM 4169) for the vial adapter
8. All of the functional verification testing in table 3 of 3.2.P.7.3
9. You briefly mention the vial adapter is cleared under a 510(k) but there you have not provided that number or included a letter of authorization for the 510k

Reviewer's Note: The sponsor has provided a response to our deficiencies in the IR response on April 28, 2017 (eCTD 0013). The sponsor did not include a LOA so this was requested again. The sponsor responded with an update to the eCTD.

VII. Outstanding Deficiencies

None.

VIII. Post-Market Commitments / Post-Market Requirements

None

IX. Recommendation

Approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON

07/13/2017

entering into Sx on behalf of CDRH Rvw team (they have electronically signed document already)

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208845

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Zilretta (Triamcinolone Acetonide) for Extended-Release Injectable Suspension

Applicant: Flexion

Receipt Date: 12/8/16

Goal Date: 10/6/17

1. Regulatory History and Applicant's Main Proposals

The firm submitted their application on 12/8/16 for a reconstitutable form of triamcinolone intended to be injected intra-articularly for the treatment the pain of osteoarthritis of the (b) (4). The product comes in a package with the diluent and a vial adaptor, making the product a combination drug-device.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by 3/7/17. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The margin on the right is less than 1/2 inch.*

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

| Heading | Required/Optional |
|---------|-------------------|
|---------|-------------------|

Selected Requirements of Prescribing Information

| | |
|---|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a BOXED WARNING is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state "None.") |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Four-digit year not included. Sponsor should add "1958" as that is the year the active ingredient (triamcinolone) was first approved in the US.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

N/A

Selected Requirements of Prescribing Information

13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- NO** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment: Sponsor phone # left out. Should be added.

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment: Date left blank. Will need to be updated with approval.

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|--|
| BOXED WARNING |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery") |
| 8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers") |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[*see Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

KIMBERLY A COMPTON
02/21/2017