

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207174Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: January 22, 2016

To: Meghna Jairath, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207174
OPDP labeling comments for PARICALCITOL INJECTION, for intravenous use

On January 20, 2016, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) for PARICALCITOL INJECTION, for intravenous use. OPDP's comments on the proposed draft PI are based on the version sent by Meghna Jairath via email on January 20, 2016 and are marked on the version provided directly below.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
01/22/2016

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: November 23, 2015
Requesting Office or Division: Division of Metabolism and Endocrinology (DMEP)
Application Type and Number: NDA 207174
Product Name and Strength: Paricalcitol injection,
2 mcg/ml, 5 mcg/ml, 10 mcg/2 ml (5 mcg/ml)
Submission Date: August 5, 2015
Applicant/Sponsor Name: Accord Healthcare Inc.
OSE RCM #: 2015-1873
DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the container labels, carton labeling, and Prescribing Information labeling for Paricalcitol (Appendix A) to determine if it is acceptable from a medication error perspective. The labels and labeling were submitted on January 29, 2015 in a previous review cycle.

2 CONCLUSION

The container labels and carton labeling for Paricalcitol is acceptable from a medication error perspective. However, we have recommendations for Section 16 How Supplied/Storage and Handling of the Full Prescribing Information labeling to improve the clarity of storage for the single-dose and multi-dose vials.

3 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

- A. In the subsection titled 'Storage' of Section 16 How Supplied/Storage and Handling of the Prescribing Information labeling, the instructions state "Discard unused portion of the single-dose vial. The opened (in use) should be stored at room temperature 20° to 25° C (68° to 77° F) and protected from light. Discard seven days after being open." To improve clarity between the different storage requirements for single-dose vials and multi-dose vials of Paricalcitol, we recommend revising the statement to as follows:
"Discard unused portion of the single-dose vial. The opened (in use) *multi-dose vial* should be stored at room temperature 20° to 25° C (68° to 77° F) and protected from light. Discard seven days after being open."

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/s/

MISHALE P MISTRY
11/23/2015

YELENA L MASLOV
11/24/2015

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

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

Memorandum

Date: January 28, 2015

To: Meghna Jairath, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207174
PARICALCITOL INJECTION, for intravenous use

OPDP has reviewed the proposed draft prescribing information (PI) for PARICALCITOL INJECTION, for intravenous use (paricalcitol) submitted for consult on May 14, 2014.

OPDP has no comments on the proposed draft PI located in Sharepoint on January 27, 2015, entitled, "NDA 207174 final PI1_23_15.doc" and provided directly below.

Thank you for the opportunity to comment on this label.

If you have any questions, please contact Kendra Jones at 301-796-3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
01/28/2015

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Names & Addresses: 1)



2)

EI Dates: August 28-29, 2014

Inspection Participants: National GLP Compliance Monitoring Authority (NGCMA), India

Inspection Summary

The current PDUFA FY2014 GLP Directed Inspection was conducted solely by a member of the India NGCMA at the request of the Division of Metabolism and Endocrinology Products (DMEP). One study, Study No. 411-1-02-7977, was audited during the inspection. The NGCMA inspector noted three observations at the conclusion of the inspection: 1) the study director did not approve a protocol amendment before the listed activities were completed; 2) bioanalytical study samples were verified, checked and signed by the same individual involved in the conduct of the study; and 3) the Ethics Committee approved the study with a slightly different study title. These observations do not substantially impact the quality and integrity of data generated for Study No. 411-1-02-7977. Therefore, this reviewer recommends that data from this study be accepted for further Agency review.

Study Audited During This Inspection

Study No.: 411-1-02-7977
Study Title: Repeated Dose 28-Day Toxicity Study of Paricalcitol Injection with Toxicokinetics through Intravenous Bolus Injection in Wistar Rats
Study Initiation Date: December 12, 2013
Study Completion Date: March 22, 2014
Test Article: Paricalcitol
Sponsor: [Redacted] (b) (4)
NDA Number : 207174
Review Division: Division of Metabolism and Endocrinology Products (DMEP)

Background: [Redacted] (b) (4) is a Contract Research Organization and nonclinical testing facility which has been certified as GLP compliant by the NGCMA since [Redacted] (b) (4). The NGCMA re-certified the firm as GLP compliant in [Redacted] (b) (4) in the following areas of expertise: Physical-chemical testing; toxicity studies; mutagenicity studies; environmental toxicity studies on aquatic and terrestrial organisms; behavioral studies conducted in water, soil and air; bioaccumulation studies; residue studies; analytical and clinical chemistry

testing; bioanalytical work; and toxicokinetics. Approximately (b) (4)% of the firm's GLP study workload involves human drugs, and is, therefore, relevant to CDER.

(b) (4) is a bioanalytical test site for Study No. 411-1-02-7977 conducted by (b) (4). The site is not a member of the National GLP compliance monitoring program, and therefore, is not monitored by the NGCMA for GLP compliance.

Prior Inspection: The NGCMA last inspected the (b) (4) for GLP compliance sometime in (b) (4) and the firm was certified as GLP compliant.

Current Inspection: The primary focus of the current FY2014 PDUFA GLP Directed Inspection conducted by the NGCMA at the request of the FDA was to verify that Study No. 411-1-02-7977 was conducted in compliance with the OECD Principles of GLP. The study plan, raw data and study report were audited. The study director, QA personnel and all personnel who actively participated in the study were interviewed by the NGCMA.

The NGCMA noted three observations during the inspection: 1) the study director approved study Protocol Amendment 3 after the activities cited in that amendment were completed for the study, 2) bioanalytical study samples were verified, checked and signed by the same individual involved in the conduct of the study at (b) (4) and 3) although the audited study title of the final report was "Repeated dose 28-day toxicity study of paricalcitol injection with toxicokinetics through intravenous injection in Wistar rats", the title of the study approved by the Ethics Committee was "Repeated dose 28-day toxicity study for paricalcitol injection using a head-to-head comparison between the test product and the reference drug product with toxicokinetics through IV route in Wistar rats".

OSI Evaluation of Inspection Findings: None of the observations cited above by the NGCMA in their inspection report substantially impact the quality and integrity of data generated for Study No. 411-1-02-7977 or the study outcome.

Recommendations

This Reviewer recommends that the data from Study No. 411-1-02-7977 be accepted for further Agency review.

Abhijit Raha, Ph.D.,
Pharmacologist, OSI-DBGLPC

Date Assigned: May 23, 2014

Inspection Type: Routine Surveillance Directed
FDA-483 Issued: Not applicable (because the NGCMA solely conducted the inspection)
Letter Issued: Not applicable (because the NGCMA solely conducted the inspection)

1st Draft Review Completed: 1/8/2015

cc: via DARRTS

OSI/Kassim

OSI DBGLPC/Taylor/Bonapace/ChenZ/Raha/Dejernett/Nkah/Fenty-Stewart/Johnson

DMEP/Parvaneh Espandari/Toxicologist (NDA 207174)

DMEP/Julie C. Van Der Waag/Regulatory Project Manager (NDA 207174)

Draft: AR 01/08/2015

Edits: ZC 1/8/2015; CB 1/8/2015

OSI File: [REDACTED] (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice
Compliance/INSPECTIONS/GLP Program/ [REDACTED] (b) (4)

[REDACTED]/FY2014/ REVIEW (EIR COVER)

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/s/

ABHIJIT RAHA
01/09/2015

ZHOU CHEN
01/09/2015

CHARLES R BONAPACE
01/09/2015

WILLIAM H TAYLOR
01/09/2015

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: December 2, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 207174
Product Name and Strength: Paricalcitol injection,
2 mcg/ml, 5 mcg/ml, 10 mcg/2 ml (5 mcg/ml)
Submission Date: December 2, 2014
Applicant/Sponsor Name: Accord Healthcare, Inc.
OSE RCM #: 2014-728-1
DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels and carton labeling is acceptable from a medication error perspective.

¹ Mistry M. Label and Labeling Review for PRODUCT NAME (NDA 207174). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 NOV 14. 15 p. OSE RCM No.: 2014-728.

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/s/

MISHALE P MISTRY
12/02/2014

YELENA L MASLOV
12/03/2014

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: November 14, 2014

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 207174

Product Name and Strength: Paricalcitol injection,
2 mcg/ml, 5 mcg/ml, 10 mcg/2 ml (5 mcg/ml)

Product Type: Single ingredient product

Rx or OTC: Rx

Applicant/Sponsor Name: Accord Healthcare, Inc.

Submission Date: April 1, 2014 (Container label and carton labeling)
June 20, 2014 (Prescribing Information labeling)

OSE RCM #: 2014-728

DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH

DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the container labels and carton labeling (submitted on April 1, 2014), and Prescribing Information (submitted on June 20, 2014) for Paricalcitol injection, NDA 207174. The Division of Metabolism and Endocrinology Products (DMEP) requested that DMEPA review the revised labels and labeling for areas of vulnerability that may lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	N/A
ISMP Newsletters	D
Other	N/A
Labels and Labeling	E

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA analyzed medication error cases that occurred with the reference listed drug, Zemplar injection. We identified medication error cases that reported wrong route of administration, wrong dose (overdose), wrong drug errors, and wrong technique errors. A review of the currently approved Zemplar Prescribing Information demonstrates that the product contains clear information regarding the dose, but the route of administration is not explicitly stated in the Dosage and Administration section. See Appendix B for additional details regarding medication error cases and our analysis of the cases.

DMEPA also searched the Institute for Safe Medication Practices (ISMP) newsletters and identified one medication error case reporting a wrong drug error between Zemplar and Fosphenytoin. However, the case is not relevant to this review because the proposed packaging for Paricalcitol does not appear similar to that of Fosphenytoin.

Additionally, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We note that the proposed container and carton labels and labeling and Prescribing Information can be improved to explicitly highlight the unique route of administration and the warning statement to not inject the drug product directly into a vein. Furthermore, we recommend decreasing the prominence of

the net quantity statement and relocating the Rx only statements on the vial label and carton labeling as to not compete in prominence with other important information. We also recommend increasing the prominence of the (b) (4) statements to ensure safe handling and appropriate use of Paricalcitol. Finally, we recommend including additional storage information on the labels and labeling of multiple-dose vials in order to prevent errors associated with using expired drug products.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and to highlight the route of administration, to promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

A. Highlights of Prescribing Information

1. Given the drug product's high alcohol content (35% v/v), explicitly state the route of administration in Section 2 Dosage and Administration, in order to highlight the unique route of administration and the importance of not injecting the drug product directly into a vein. Suggested language may include:

"CKD Stage 5: The recommended initial dose of paricalcitol injection is 0.04 mcg/kg to 0.1 mcg/kg (2.8 to 7 mcg) administered through a hemodialysis vascular access port as a bolus dose no more frequently..."

2. Include the 10 mcg/2 mL presentation in Dosage Forms and Strengths section. Suggested language may include:

"Injection: 2 mcg per mL, 5 mcg per mL, and 10 mcg per 2 mL (5 mcg per mL) (3)."

B. Full Prescribing Information

1. Given the drug product's high alcohol content (35% v/v), explicitly state the route of administration in Section 2 Dosage and Administration, in order to highlight the unique route of administration and the importance of not injecting the drug product directly into a vein. Suggested language may include:

"The recommended initial dose of paricalcitol injection is 0.04 mcg/kg to 0.1 mcg/kg (2.8 to 7 mcg) administered through a hemodialysis vascular access port as a bolus dose no more frequently..."

Additionally, to draw health care professionals' attention to this unique route of administration, include the following statement in bolded text at the beginning of Section 2 Dosage and Administration:

"For intravenous use through hemodialysis vascular access port only"

2. Include the 10 mcg/2 mL presentation in Section 3 Dosage Forms and Strengths section. Suggested language may include:

“Paricalcitol injection is available as 2 mcg per mL, 5 mcg per mL, and 10 mcg per 2 mL (5 mcg per mL) vials as clear, colourless solution.”

3. Include the 10 mcg/2 mL presentation in Section 16 How Supplied/Storage and Handling section. Suggested language may include:

“ Paricalcitol injection is available as 2 mcg per mL (NDC 16729-310-63), 5 mcg per mL (NDC 16729-311-63), and 10 mcg per 2 mL (5 mcg per mL)(NDC 16729-311-30) in carton of 1 vial.”

4. Revise the Table in Section 16 How Supplied/Storage and Handling section to clearly display the strength per total volume and reflect current terminology. For example:

NDC No.	Total Content/ Concentration	Volume/Container	Vial Type
16729-310-63	2 mcg/mL	1 mL	Single-dose
16729-311-63	5 mcg/mL	1 mL	Single-dose
16729-311-30	10 mcg/2 mL (5 mcg/mL)	1 mL	Multi-dose

5. Revise the storage information in Section 16 How Supplied/Storage and Handling section to include the following information, currently located in Section 2 Dosage and Administration:

“After initial vial use, the contents of the multi-dose vial remain stable up to seven days when stored at controlled room temperature. Discard unused portion of the single-dose vial.”

4.2 RECOMMENDATIONS FOR ACCORD HEALTHCARE, INC.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Vial label

1. Per FDA’s Guidance for Industry ¹, relocate the “Rx Only” statement to the bottom of the vial label so that the statement does not compete with other important information on the label.
2. Per FDA’s Guidance for Industry ², decrease the prominence of the net quantity statement to mitigate the risk of dosing errors where the net quantity is mistaken for the product strength.

¹ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Nov 7]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. “Other information on the PDP such as the Rx-only statement, net quantity statement, manufacturer name, and logo should not compete in size and prominence with the important information listed above [proprietary name, established name or proper name, product strength, route(s) of administration, warnings (if any) or cautionary statements (if any).”

² See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Nov 7]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

3. Given the drug product's high alcohol content (35% v/v), revise the statement "(b) (4)" in order to highlight the unique route of administration and the importance of not injecting the drug product directly into a vein. Suggested language may include:

"For intravenous use through hemodialysis vascular access port only"

4. **2 mcg/mL, 5 mcg/mL vial label:**

- i. To ensure safe handling and appropriate use of the drug product, increase the prominence (size) of the following statement:

"Single-Dose Vial. Discard unused portion"

B. Carton labeling

1. Per FDA's Guidance for Industry ¹, relocate the "Rx Only" statement to the bottom of the Principal Display Panel (PDP) so that the statement does not compete with other important information on the label.

2. Given the drug product's high alcohol content (35% v/v), revise the statement "(b) (4)" on the PDP and back panel in order to highlight the unique route of administration and the importance of not injecting the drug product directly into a vein. Suggested language may include:

"For intravenous use through hemodialysis vascular access port only".

Additionally, increase the prominence (size) of this statement on the PDP.

3. Consider removing route of administration statement from back panel as this information is repetitive.

4. **2 mcg/mL, 5 mcg/mL carton labeling:**

- i. To ensure safe handling and appropriate use of the drug product, revise the statement "Single-Dose Vial" to the following and increase its prominence (size):

"Single-Dose Vial. Discard unused portion.

- ii. Consider revising the net quantity statement "(b) (4)" to "1 mL vial" to decrease clutter and extraneous text.

5. **10 mcg/2 mcg carton labeling:**

- i. The expiration date differs from that of typical multiple-dose vials where the product should be discarded within (b) (4) days after initial use. To prevent errors associated with using expired drug products, revise the storage information statement on the back panel to include the following information:

"After initial use, discard within 7 days when stored at controlled room temperature."

- ii. Consider revising the net quantity statement "(b) (4)" to "2 mL vial" to decrease clutter and extraneous text.

"The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)."

iii. APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paricalcitol that Accord Healthcare, Inc. submitted on April 1, 2014 and June 20, 2014, and the reference listed drug (RLD).

Table 2. Relevant Product Information for Paricalcitol and the Reference Listed Drug		
Product Name	Paricalcitol	Zemplar (RLD)
Initial Approval Date	N/A	April 17, 1998
Active Ingredient	Paricalcitol	
Indication	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5	
Route of Administration	Intravenous	
Dosage Form	Solution for injection	
Strength	2 mcg per mL 5 mcg per mL 10 mcg per 2 mL (5 mcg per mL)	
Dose and Frequency	Initial dose: 0.04 mcg/kg to 0.1 mcg/kg (2.8 mcg – 7 mcg) administered as a bolus dose no more frequently than every other day at any time during dialysis. Adjust dose: dose may be increased by 2 mcg to 4 mcg at 2- to 4-week intervals.	
How Supplied	Single-dose vials: 2 mcg per mL 5 mcg per mL Multi-dose vials: 10 mcg per 2 mL	Single-dose vials: 2 mcg per mL 5 mcg per mL 10 mcg per 2 mL Multi-dose vials: 10 mcg per 2 mL
Storage	Store at 25°C (77°F). Excursions permitted between 15° to 30°C (59° to 86°F). After initial vial use, the contents of the multi-dose vial remain stable up to seven days when stored at controlled room temperature. Discard unused portion of the single-dose vial.	Store at 25°C (77°F). Excursions permitted between 15°C - 30°C (59°F - 86°F).
Container Closure	1-ml and 2-ml flip-top vials	

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

DMEPA previously performed a search of the FDA Adverse Event Reporting System (FAERS), reported in OSE Review #2013-2112 (dated May 28, 2014) and OSE Review #2014-913 (dated September 11, 2014) to determine medication errors related to the use of this product.³ Therefore, for this review, we searched FAERS on November 7, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁴

Date Range	August 1, 2014 to November 1, 2014
Product	Paricalcitol [active ingredient]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our current search from August 1, 2014 to November 1, 2014 identified four cases, two of which described errors relevant for this review. We excluded two cases because they described errors associated with Zemplar capsules.

Following exclusions, two cases (FAERS Case # 10477975 [v1], FAERS Case # 10477976 [v1]) remained for further analysis:

Wrong route of administration (n=1)

- One case (FAERS Case # 10477975 [v1]) reported a patient who received Zemplar subcutaneously, in the deltoid region of the arm, instead of intravenously. The patient did not experience any adverse events as a result of subcutaneous administration. No additional details were provided regarding contributing factors.

A review of the currently approved Zemplar® Prescribing Information labeling and proposed Prescribing Information labeling for Paricalcitol identified that the route of administration is not

³ Gao T. Label and Labeling Review for Paricalcitol (NDA 205917). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May 28. 13 p. OSE RCM No.: 2013-2112.

Mistry M. Label and Labeling Review for Paricalcitol (NDA 201657). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Sept 11. 16 p. OSE RCM No.: 2014-913.

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

explicitly stated in the Dosage and Administration section. Therefore, we note that the Prescribing Information labeling can be improved to further highlight the route of administration.

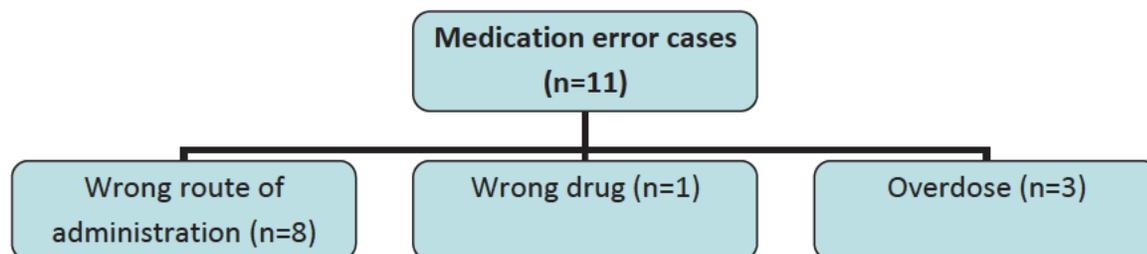
Wrong technique (n=1)

- One case (FAERS Case # 10477976 [v1]) reported that a health care professional used the same needle and syringe to enter two medication vials of Zemplar. No additional details were provided regarding contributing factors or patient outcome as a result of the medication error.

A review of the currently approved Zemplar® Prescribing Information labeling does not explicitly state that different needles should be used when entering more than one medication vial. However, such practices are considered safe practices for medical injections and are generally recommended for medication preparation.

The previous FAERS searches were conducted in OSE Review #2013-2112 (dated May 28, 2014) and OSE Review #2014-913 (dated September 11, 2014), and provided a detailed analysis of 11 medication error cases, following exclusions. Duplicates were merged into a single case, and one case described two different types of medication errors, resulting in 12 medication error cases for analysis. Figure 1 provides a stratification of the number of cases included in the previous reviews (OSE Review #2013-2112, OSE Review #2014-913) by type of error.

Figure 1. Paricalcitol Medication Errors (n=12), categorized by type of error (OSE Review # 2013-2112)



Wrong route of administration (n=8)

- One case, FAERS Case # 7905193 [v1], reported a patient who received Zemplar 1 ml intramuscularly instead of intravenously. The patient complained that the injection hurt and the pain resolved after the medication was administered. The error may have occurred due to patient getting a hepatitis B vaccine intramuscularly prior to the Zemplar injection, but no additional information was provided regarding contributing factors.
- Seven cases reported the administration of Zemplar subcutaneously rather than intravenously. In four of the cases [FAERS Case # 6540808 [v1], 6639997 [v1], 6998766 [v1], 8011161 [v1]], the patients experienced injection site reactions (stinging, redness, tissue necrosis) and hypocalcemia, whereas the outcomes for the other three cases (FAERS Case # 7905181 [v1], 7905187 [v1], 10084015 [v1]) were not provided. In one of the cases (FAERS Case # 7905181 [v1]) where the patient received Zemplar subcutaneously, we attributed the wrong route error to the fact that patient was supposed to receive Epogen subcutaneously but received Zemplar subcutaneously in error. No additional information was provided regarding contributing factors for the other cases.

A review of the currently approved Zemplar® Prescribing Information labeling and proposed Prescribing Information labeling for Paricalcitol identified that the route of administration is not explicitly stated in the Dosage and Administration section.

Wrong drug (n=1)

- One case, FAERS Case # 7905181 [v1], reported a patient who received Zemplar (2 mcg/mL, 1 mL vial) instead of Epogen while on dialysis at home. The reporter stated that the patient’s mother confused the vial of Zemplar with that of Epogen and intended to inject the patient with Epogen via subcutaneous route. Patient experienced hypocalcemia and Zemplar was discontinued.

A review of the vial labels of Zemplar and Epogen indicate that there are differences between the labels that differentiate the two drug products. Therefore, we not believe revisions to the label are needed at this time.

Overdose (n=3)

- One case, FAERS Case # 6605665 [v1], reported an overdose resulting in hypercalcemia because patient’s Zemplar dose was not adjusted despite an increase in calcium and parathyroid hormone (PTH) levels. No additional information was provided regarding contributing factors or patient outcome as a result of the medication error.
- One case, FAERS Case # 7905183 [v1], reported an overdose where the patient received 23 mcg instead of 3 mcg. Patient experienced cramping all over during the patient’s dialysis that was resolved when the patient was given saline. This error occurred because the person entering the dose accidentally wrote 23 mcg instead of 3 mcg. Therefore, this error does not appear to be associated with the label and labeling of the product.
- One case, FAERS Case # 9236063 [v1], reported an overdose where the patient received 20 mcg/4 mL instead of 4 mcg/0.8 mL. No patient outcome was reported for this error. This error might have occurred due to confusion between 4 mcg and 4 mL. However, this error does not appear to be associated with the label and labeling of the proposed product.

Although we identified three medication errors reporting overdose, a review of the Dosage and Administration section within the currently approved Zemplar® Prescribing Information labeling indicates that the labeling contains clear information regarding dosing of Zemplar. As a result, we do not believe revisions to the labeling are needed at this time.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Table 4: Identified FAERS Case Numbers and Corresponding Manufacturer Control Numbers Summarized in Review		
FAERS Case Number	Version	Manufacturer Control Number
<i>Current Review – OSE Review # 2014-728</i>		
10477975	1	US-ABBVIE-14P-163-1205877-00
10477976	1	US-ABBVIE-14P-163-1211515-00

<i>OSE Review # 2014-913</i>		
10084015	1	US-ABBVIE-13P-163-1136240-00
<i>OSE Review # 2013-2112</i>		
6540808	1	US-ABBOTT-08P-163-0434913-00
6605665	1	SE-ABBOTT-08P-150-0444481-00
6639997	1	US-ABBOTT-07P-163-0374203-00
6998766	1	US-ABBOTT-09P-163-0561156-00
7905181	1	US-ABBOTT-11P-163-0704486-00
7905183	1	US-ABBOTT-10P-163-0659344-00
7905187	1	US-ABBOTT-11P-163-0704868-00
7905193	1	US-ABBOTT-10P-163-0647838-00
8011161	1	US-ABBOTT-07P-163-0376072-00
9236063	1	US-ABBOTT-12P-163-0928566-00

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on November 7, 2014 using the term, Paricalcitol to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified three previous Paricalcitol reviews.⁵

⁵ Mistry M. Label and Labeling Review for Paricalcitol (NDA 201657). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Sept 11. 16 p. OSE RCM No.: 2014-913.

Gao T. Label and Labeling Review for Paricalcitol (NDA 205917). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May 28. 13 p. OSE RCM No.: 2013-2112.

Baugh D. Label and Labeling Review for Paricalcitol (NDA 201657). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2011 Dec 06. 20 p. OSE RCM No.: 2011-1771.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on November 7, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Paricalcitol

D.2 Results

Our search identified one article described an error associated with a mixup of a vial of Zemplar (paricalcitol) 5 mcg/mL and a vial of fosphenytoin 100 mg PE/2 mL due to its look-alike packaging. Both vials have a (b) (4) flip-top cap with a (b) (4) label that contains the drug name in (b) (4) font color.⁶

This case is not relevant to this review because the vial of fosphenytoin that was associated in the mixup was manufactured by Hospira, the drug name on the *proposed* vial labels appears prominent in size and bold-faced font, and the packaging does not look similar.

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

⁶ Institute for Safe Medication Practices. Safety briefs: Look-alike vials. ISMP Med Saf Alert Acute Care. 2008;13(4):1.

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

/s/

MISHALE P MISTRY
11/14/2014

YELENA L MASLOV
11/17/2014

M E M O R A N D U M

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

DATE: May 22, 2014

TO: William H. Taylor, Ph.D., Director
Division of Bioequivalence and Good Laboratory
Practice (GLP) Compliance (DBGLPC)
Office of Scientific Investigations (OSI)
Office of Compliance (OC)
Center for Drug Evaluation and Research (CDER)

THROUGH: Charles R. Bonapace, Pharm.D.
Acting Branch Chief
Good Laboratory Practice (GLP) Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)
Office of Compliance (OC), CDER

FROM: Abhijit Raha, Ph.D., Pharmacologist
Good Laboratory Practice (GLP) Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)
Office of Compliance (OC), CDER

SUBJECT: **FY2014, PDUFA GLP Directed Inspections of** (b) (4)
Bioresearch Monitoring, Human Drugs,
CP 7348.808

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Office of Scientific Investigations (OSI) requests that arrangements be made for a directed GLP inspection of the following two firms in (b) (4):

FIRM #1:
ADDRESS:

FIRM'S CONTACT:

PHONE:
MOBILE:
FAX:
EMAIL ADDRESS:

(b) (4)

[REDACTED]

FIRM #2:

ADDRESS:

FIRM'S CONTACT:

PHONE:

MOBILE:

FAX:

EMAIL ADDRESS:

[REDACTED] (b) (4)

This inspection will be performed by inspectors from the National GLP Compliance Monitoring Authority (NGCMA) under their OECD (Organization for Economic Co-operation and Development) monitoring authority. **Because of the NDA application deadline, we request that the inspection be completed prior to** [REDACTED] (b) (4)

[REDACTED].

The following nonclinical study, conducted in accordance to Good Laboratory Practice Principles as published by the OECD in 1998, should be audited in this inspection.

Study Number: 411-1-02-7977
Study Title: "Repeated Dose 28-Day Toxicity Study of Paricalcitol Injection with Toxicokinetics Through Intravenous Bolus Injection in Wistar Rats"
Test Article: Paricalcitol
Study Initiation Date: December 12, 2013
Study Completion Date: March 22, 2014
Sponsor: Accord Healthcare, Inc. (Durham, NC)
Relevant FDA Submission: NDA 207-174

Preannouncement of the study that will be inspected should NOT be made to the firm.

OSI CONTACTS: Arindam Dasgupta, Ph.D. (DFFI Contact)
301-796-3326
arindam.dasgupta@fda.hhs.gov

Abhijit Raha, Ph.D. (Secondary Contact)
301-796-3708
abhijit.raha@fda.hhs.gov

Please contact OSI at least 30 days prior to the planned inspection start date to discuss assignment details and obtain pertinent background materials.

All pertinent items related to Study Number 411-1-02-7977 should be examined and the data should be audited at (b) (4)

The protocol and actual in-life study conduct and bioanalytical raw data, respectively, should be compared to the data presented in the final study report. Furthermore, Quality Assurance Unit (QAU) monitoring, maintenance and calibration of pertinent equipment relevant to the study, and the (b) (4) archiving practices should be examined. The Standard Operating Procedures (SOPs) for the various procedures need to be scrutinized. In addition to the standard audit involving various source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Applicable exhibits (e.g. SOPs, raw data sheets) should be collected for all findings to assess the impact of the findings.

The source records and final study report for Study 411-1-02-7977 at the inspection site should be compared with the final study report submitted to FDA for inconsistencies. The impact on study outcome of each inconsistency found during the comparison should be provided.

The following issues need to be addressed during the inspection:

- What percentage of (b) (4) GLP workload is related to human drugs?
- Does (b) (4) outsource any study phases, e.g., analysis of dosing formulations and histopathologic evaluations?
- Document how QAU oversight is assured for the outsourced phases and for the study portions conducted at (b) (4).
- Does the final report identify the facilities that conducted the outsourced phases? Please collect a list of all firms used by (b) (4) for outsourced phases.
- Did the study director sign and date protocol amendments on or before the day when procedures were actually changed?
- Does (b) (4) submit signed and dated contributing scientist reports to the study director?

- Were the results of test article characterization and dosing formulation analyses reported to the study director and included in the final study report?
- Were signed and dated contributing scientists' reports, attached to the final report?
- If applicable, have deficiencies identified by the NGCMA from the previous inspection been corrected? Have the corrective actions prevented recurrence of the deficiencies?

cc:

CDER OSI PM TRACK

DMEP/Parvaneh Espandiari/Toxicologist

DMEP/Julie C. Van Der Waag/Regulatory Project Manager

OSI/DBGLPC/Taylor/Bonapace/ChenZ/Li/Dasgupta/Raha/CF

Draft: AR 5/21/2014

Edit: ZC 5/22/2014; CB 5/23/2014

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good

Laboratory Practice Compliance/Inspections/GLP Program/ (b) (4)

/FY2014/ASSIGNMENT

GLP File No.: (b) (4)

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

/s/

ABHIJIT RAHA
05/23/2014

ZHOU CHEN
05/23/2014

CHARLES R BONAPACE
05/23/2014

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

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

Application: NDA 207174

Application Type: New NDA

Name of Drug/Dosage Form: paricalcitol injection

Applicant: Accord Healthcare, Inc.

Receipt Date: April 1, 2014

Goal Date: February 1, 2015

1. Regulatory History and Applicant's Main Proposals

This is a 505(b)(2) NDA relying on FDA's previous finding of safety and efficacy for NDA 20819 for Zemplar.

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 for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format within 3 weeks. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-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 A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 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:

- NO** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Highlights is longer than 1/2 page.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 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

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Need to remove white space between product title and Initial U.S. Approval.*

- 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. Section headings must be presented in the following order in HL:

Section	Required/Optional
• 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 the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- NO** 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: *Name of drug should appear in upper case letters.*

Product Title in Highlights

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

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading 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 should be centered immediately beneath the heading 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 heading 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 the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in 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) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Established pharmacologic class is vitamin ^{(b) (4)} analog.*

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. 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) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. 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** 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** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Present, but will need to be updated prior to approval.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. 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** 27. The same heading 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** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. 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 (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- Yes** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of 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

- YES** 32. 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 Labor and Delivery
8.3 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** 33. 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)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A 36. In the BW, all text should be **bolded**.
- N/A 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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: *This statement is missing.*

- NO 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), 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: *This statement is missing.*

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) 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 A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 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
- 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 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

JULIE C VAN DER WAAG
05/15/2014

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 # 207174 BLA#	NDA Supplement #:S- N/A BLA Supplement #	Efficacy Supplement Type SE- N/A
Proprietary Name: none submitted Established/Proper Name: paricalcitol Dosage Form: injection Strengths: 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL and 2 mL)		
Applicant: Accord Healthcare, Inc. Agent for Applicant (if applicable): None		
Date of Application: April 1, 2014 (gateway) March 31, 2014 (letter and Form 356h) Date of Receipt: April 1, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: February 1, 2015		Action Goal Date (if different): January 30, 2015
Filing Date: May 31, 2014		Date of Filing Meeting: May 14, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Paricalcitol injection is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5		
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): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input 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)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <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 [21 CFR 314.55(b)/21 CFR 601.27(b)] <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 (<i>if OTC product</i>):				
List referenced IND Number(s): PIND 113078				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <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 proprietary, established/proper, and applicant names correct in tracking system? <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 tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, 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"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><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. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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> <p><i>If you answered yes to any of the above 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</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <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													<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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 will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
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)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<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"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</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	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<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)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <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) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<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. Forms include: user fee cover sheet (3397), 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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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 type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input type="checkbox"/>	<input checked="" type="checkbox"/>		No clinical studies

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><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></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Correctly worded debarment certification submitted on May 2, 2014.
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> 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><u>For non-NMEs:</u> <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
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<u>Proprietary Name</u>	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 type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>REMS</u>	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"/>	
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <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 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"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<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?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) 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)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): November 29, 2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-IND/Pre-NDA meeting
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 14, 2014

BLA/NDA/Supp #: 207174

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: paricalcitol

DOSAGE FORM/STRENGTH: injection

APPLICANT: Accord Healthcare Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Paricalcitol injection is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:		
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Dragos Roman		Y
Clinical	Reviewer:	Naomi Lowy	Y
	TL:	Dragos Roman	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:	Immo Zadezensky	N
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Parvaneh Espandiari	N
	TL:	Karen Davis-Bruno	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xavier Ysern	N
	TL:	Su Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Amarylis Vega	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Kendra Jones (OPDP), Yelena Maslov (OSE), Mishale Mistry (OSE)		Y
Other attendees	Terrolyn Thomas (OSE), Steve Hertz (OMPQ)		

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., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO A bridging nonclinical toxicology study was conducted.
<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 No comments
<p>CLINICAL</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
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" 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"> 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
<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>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
<p>CLINICAL PHARMACOLOGY</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
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></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><u>CMC Labeling Review</u></p> <p>Comments:</p>	<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: Jean-Marc Guettier	

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

21st Century Review Milestones

- Day 74 Letter Date: June 13, 2014
- Team Meeting #1 (can be cancelled if not needed): July 14, 2014
- Mid-Cycle Review Meeting: September 8, 2014
- Team Meeting #2 (can be cancelled if not needed): October 14, 2014
- First Labeling Meeting: December 2, 2014
- Draft Reviews Due to Team Leaders: December 12, 2014
- Wrap-Up Meeting: December 16, 2014
- Primary Reviews Due in DARRTS: December 19, 2014
- Send Labeling/PMR/PMC to Applicant: Before January 1, 2015
- CDTL Memo Due: January 9, 2015
- PDUFA Goal Date: February 1, 2015

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

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

ACTIONS ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<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 NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

JULIE C VAN DER WAAG
05/15/2014