CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208614Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: July 19, 2018

To: William A. Lubas, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Meghna Jairath, Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

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

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for DOXERCALCIFEROL injection, for intravenous use

NDA: 208614

In response to DMEP's consult request dated February 12, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling, for the original NDA resubmission for DOXERCALCIFEROL injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI submitted electronically by the Division of Metabolism and Endocrinology on July 17, 2018 and are provided below. OPDP does not have any additional comments on the proposed labeling at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 30, 2017 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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

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/s/

CHARUNI P SHAH
07/19/2018

MEMORANDUM

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)

Date of This Review:	July 10, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208614
Product Name and Strength:	Doxercalciferol injection, 2 mcg/mL
Total Product Strength:	4 mcg/2 mL and 10 mcg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Hospira Inc. (Hospira)
FDA Received Date:	June 18, 2018
OSE RCM #:	2016-2746-2
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Hospira submitted revised carton labeling on June 18, 2018, in response to the Office of Pharmaceutical Quality's (OPQs) request to revise the storage information on the carton labeling.[a] Specifically, [redacted] (b) (4) was revised to "Store unopened vial in original carton; discard vial 14 days after opening" (Appendix A). We evaluated the revised carton labeling for areas of vulnerability that may lead to medication errors.

2 CONCLUSION

DMEPA concludes that the revised carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Hospira's Amendment received on June 18, 2018; EDR location (file link): *Application 208614 - Sequence 0009 - (CL) Response to Labeling Information Request Jun 2018* (\\cdsesub1\evsprod\nda208614\0009\m1\us\cover.pdf)

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JUNE 18, 2018

(b) (4)


(b) (4)

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/s/

SUSAN RIMMEL
07/10/2018

HINA S MEHTA
07/10/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Addendum to
Division of Pediatric and Maternal Health Memorandum

Date: June 19, 2017 **Date Reconsulted:** February 21, 2018

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Meghna M. Jairath, Pharm.D., Regulatory Project Manager (RPM)
Division of Metabolic and Endocrine Products (DMEP)

Drug: Doxercalciferol Injection

NDA: NDA 208614

Indication: Doxercalciferol Injection is a synthetic vitamin D2 analog indicated for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis

Applicant: Hospira, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's submitted background package for NDA 208614, SD#2, November 30, 2016.
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#4 on March 31, 2017.
- DPMH consult review of Doxercalciferol Injection, NDA 208614. Jane Liedtka, M.D. August 23, 2017. DARRTS Reference ID 4142431.

Consult Question: Please review PLLR labeling for this resubmission after complete response (CR).

INTRODUCTION

On February 21, 2018, DMEP reconsulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of doxercalciferol injection labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On November 30, 2016, Hospira Inc. submitted a new drug application (NDA) via the 505 B (2) pathway for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis.
- The reference listed drug (RLD) for this product is NDA 021027 for Hectorol (doxercalciferol) Injection, 2 mcg/mL approved on April 6, 2000 for the treatment of secondary hyperparathyroidism in patients with CKD on dialysis.
- On January 23, 2017, the Agency sent the Applicant an Information Request requesting that they submit a literature search and a review and summary of the Applicant's pharmacovigilance database regarding doxercalciferol injection use in pregnant and lactating women and effects on fertility.
- On March 31, 2017, the Applicant submitted the requested supporting information which appeared adequate.
- On September 14, 2017, the Agency issued a Complete Response (CR) letter. On January 26, 2018, the sponsor submitted their response to the CR.

REVIEW

The reader is referred to DPMH consult review of Doxercalciferol Injection, NDA 208614[1] for discussion of background and review of the literature for this product. DPMH has reproduced the summary for each subsection of the Pregnancy and Lactation labeling and has made slight revisions to the proposed language from that review in order to update to currently recommended language.

Summary for Pregnancy

There are no human pregnancy outcome data for doxercalciferol in the published literature. The findings in animal studies did not demonstrate any findings indicative of risk to the fetus. Based on the review of published literature in the earlier 2017 Doxercalciferol review, DPMH recommends a "Clinical Considerations" subsection be added to subsection 8.1. See DPMH proposed labeling below for further details.

[1]DPMH consult review of Doxercalciferol Injection, NDA 208614. Jane Liedtka, M.D. August 23, 2017. DARRTS Reference ID 4142431.

Summary for Lactation

There are no data on the presence of doxercalciferol in animal or human milk. Although doxercalciferol has high protein binding, the drug has other characteristics, including molecular weight <800 Daltons and a long half-life in patients with CKD, which may increase the presence of the drug in maternal circulation and may increase transfer of the drug into breastmilk. However, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk. Given all the unknowns, and the potential for elevated calcium in the breastfed infant exposed to doxercalciferol, DPMH recommends a "Clinical Considerations" subsection be added to subsection 8.2. See DPMH proposed labeling below for further details.

Summary for Use in Females and Males of Reproductive Potential

Animal reproductive studies of administration of doxercalciferol injection did not show any adverse effects on fertility. No pregnancy testing or contraception recommendations are needed. Therefore, subsection 8.3, Females and Males of Reproductive Potential, will not be included in doxercalciferol injection labeling.

LABELING RECOMMENDATIONS

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

DPMH Proposed Doxercalciferol Injection Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 Use in Specific Populations
8.1 Pregnancy
Risk Summary

There are no human data with doxercalciferol injection in pregnant women to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with chronic kidney disease in pregnancy *(see Clinical Considerations*). In reproduction studies in rats and rabbits, at doses of doxercalciferol up to 20 mcg/kg/day and 0.1 mcg/kg/day (approximately 25 times and less than the maximum recommended human oral dose of 60 mcg/week based on mcg/m^2 body surface area, respectively) administered during organogenesis, no adverse developmental effects were observed (*see Data*).

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Chronic kidney disease in pregnancy increases the risk for maternal hypertension,pre-eclampsia, miscarriage, still birth, preterm delivery , low birth weight infants, and polyhydramnios.

Data

Animal Data

There were no adverse effects on fetal growth or survival at doses up to 20 mcg/kg/day, when doxercalciferol was administered to pregnant female rats during organogenesis. When administered to pregnant female rabbits during organogenesis, there were no adverse effects on fetal growth or survival at doses up to 0.3 mcg/kg/day.

8.2 Lactation

Risk Summary

There is no information available on the presence of doxercalciferol injection in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Infants exposed to doxercalciferol injection through breast milk should be monitored for signs and symptoms of hypercalcemia *(see Clinical Considerations)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Doxercalciferol Injection and any potential adverse effects on the breastfed child from Doxercalciferol Injection or from the underlying maternal condition.

Clinical Considerations

Infants exposed to doxercalciferol injection through breast milk should be monitored for signs and symptoms of hypercalcemia, including seizures, vomiting, constipation and weight loss. Monitoring of serum calcium in the infant should be considered.

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/s/

JANE E LIEDTKA
06/19/2018

MIRIAM C DINATALE
06/19/2018

LYNNE P YAO
06/21/2018

MEMORANDUM

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)

Date of This Review:	June 12, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208614
Product Name and Strength:	Doxercalciferol injection, 2 mcg/mL
Total Product Strength:	4 mcg/2 mL and 10 mcg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Hospira Inc. (Hospira)
FDA Received Date:	January 26, 2018, and February 5, 2018
OSE RCM #:	2016-2746-1
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Metabolism and Endocrinology Products (DMEP) consulted DMEPA to evaluate the revised container labels and carton labeling for Doxercalciferol injection 2 mcg/mL (Appendix A) to determine if it is acceptable from a medication error perspective. The container labels and carton labeling revisions are in response to recommendations we made during a previous label and labeling review.[a]

1.1 REGULATORY HISTORY

Hospira submitted NDA 208614 for Doxercalciferol injection 2 mcg/mL, utilizing the 505(b)(2) regulatory pathway, on November 30, 2016. The submission proposes a 4 mcg/2 mL multi-dose vial, which is in alignment with the reference listed drug (RLD), and a new 10 mcg/5 mL multi-dose vial to provide additional dosing flexibility with less waste. The RLD is Hectorol (NDA 021027), which was approved on April 6, 2000.

The Agency issued a Complete Response (CR) letter on September 14, 2017, due to field investigators observed objectionable conditions during a facility inspection. Hospira submitted a response to the CR on January 26, 2018.

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective. We note that recommendations provided to DMEP in our prior review for the Prescribing Information (PI) are still pending consideration. Therefore, we provide recommendations for the PI to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion.

3 RECOMMENDATIONS FOR THE DIVISION

We note that recommendations provided to DMEP in our prior review for the PI are still pending consideration.[b] These recommendations are reiterated below.

A. Highlights of PI
    1. Dosage and Administration – Define the acronym “iPTH” the first time it appears in the Highlights of PI as follows: “...and based on intact parathyroid hormone (iPTH) levels with...”

B. Full PI

[a] Rimmel, S. Label and Labeling Review for Doxercalciferol NDA 208614. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 07. RCM No.: 2016-2746.

[b] Rimmel, S. Label and Labeling Review for Doxercalciferol NDA 208614. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 07. RCM No.: 2016-2746.

1. Section 2 Dosage and Administration, Section 2.1 Initial Dose and Titration – Define the acronym “iPTH” the first time it appears in the Full PI as follows: “...and based on intact parathyroid hormone (iPTH) levels with...”
2. Section 3 Dosage Forms and Strengths – Add information regarding identifying characteristics, and rephrase this section as follows:

   Injection: 4 mcg/2 mL (2 mcg/mL) or 10 mcg/5 mL (2 mcg/mL), as a clear and colorless aqueous solution in multiple-dose vials

3. Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility – For clarity and to mitigate any confusion, we recommend spelling out the intended meaning of abbreviation “wk” (e.g., revise “60 mcg/wk” to “60 mcg/week”), particularly in areas where dosing is described.
4. Section 16 How Supplied/Storage and Handling
   a. Add information regarding identifying characteristics, and rephrase the first sentence as follows: “Doxercalciferol injection is supplied as a clear, colorless aqueous solution in multiple-dose amber glass vials ...”
   b. For added clarity and to reduce confusion, revise the second sentence and table to display product information as follows:

      The closure consists of a fluorocarbon-coated chlorobutyl stopper, with an aluminum seal and plastic flip-off cap.

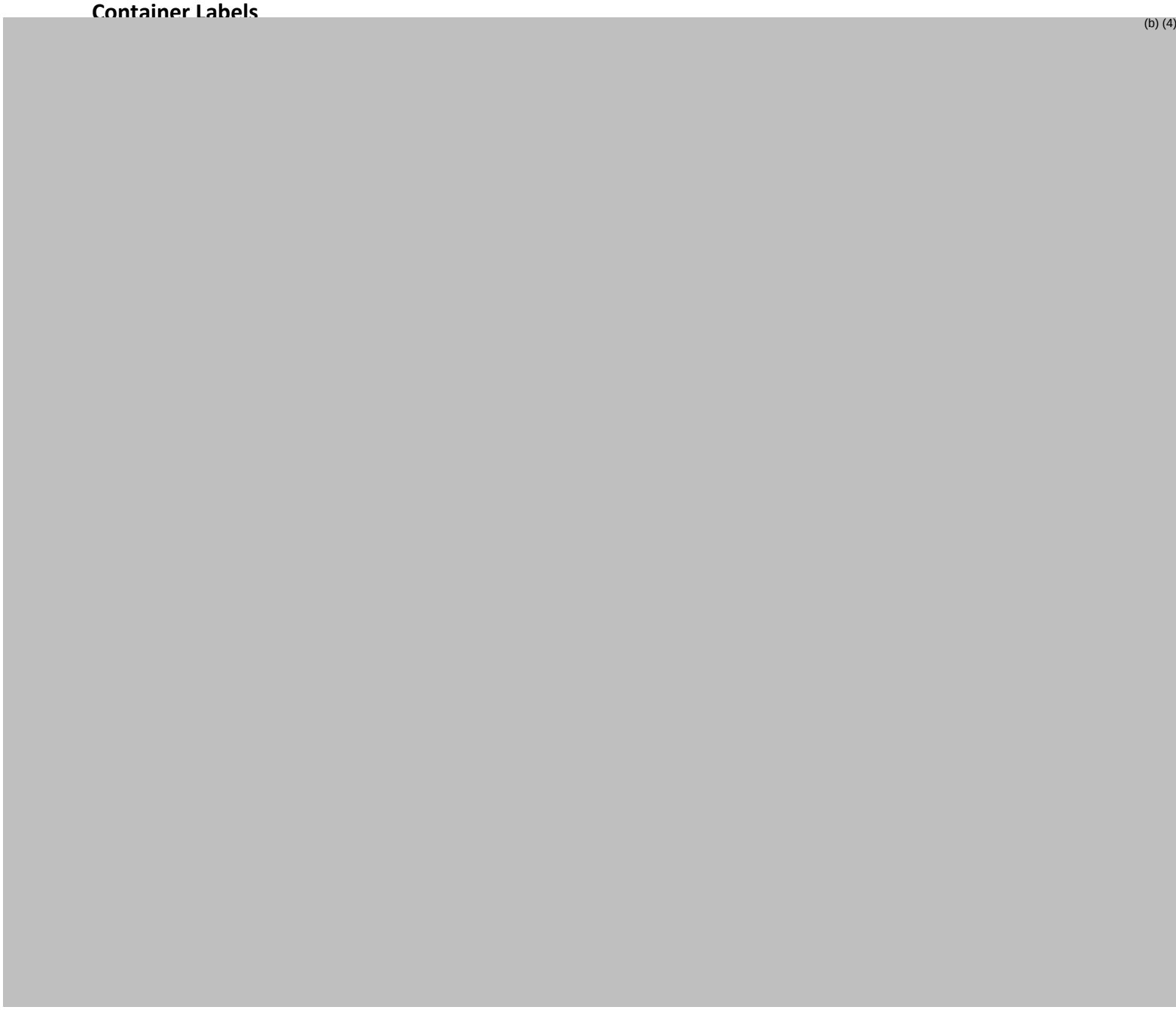
Doxercalciferol Total Product Strength (Concentration)	Flip-off Cap Color	Carton NDC and Package Configuration	Vial NDC
4 mcg/2 mL (2 mcg/mL)	Orange	0409-1330-01 50 x 2 mL multiple-dose vials	0409-1330-11
10 mcg/5 mL (2 mcg/mL)	Gray	0409-1331-01 50 x 5 mL multiple-dose vials	0409-1331-11

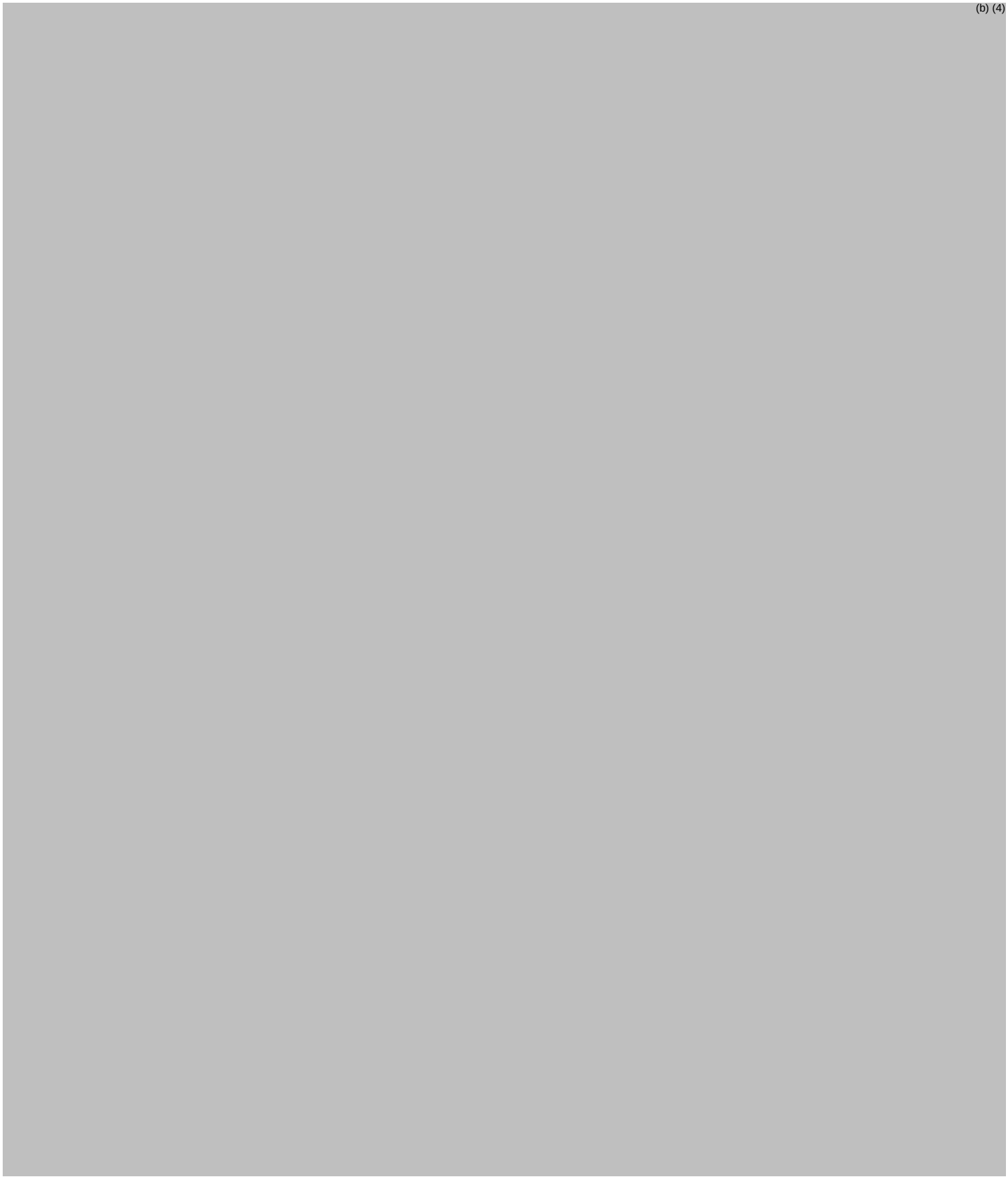
   c. Add information on storage of unopened and opened Multi-Dose Vials (i.e., Store unopened vial in original carton. Discard vial 14 days after opening.).

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JANUARY 26, 2018, AND FEBRUARY 5, 2018

Container Labels

(b) (4)




(b) (4)

Prescribing Information (image not shown; EDR location and file link)

Application 208614 - Sequence 0007 - Doxercalciferol USPI Hospira Track Changes LAB-0887-1.0 Apr 2017

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/s/

SUSAN RIMMEL
06/12/2018

HINA S MEHTA
06/12/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: August 22, 2017 **Date Consulted:** January 9, 2017

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Richard Whitehead, Regulatory Project Manager (RPM)
Division of Metabolic and Endocrine Products (DMEP)

Drug: Doxercalciferol Injection

NDA: NDA 208614

Indication: Doxercalciferol Injection is a synthetic vitamin D2 analog indicated for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis

Applicant: Hospira, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- DPMH consult request dated January 9, 2017, DARRTS Reference ID 4039010.
- Applicant's submitted background package for NDA 208614, SD#2, November 30, 2016.
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#4 on March 31, 2017.

- DPMH consult review of Zemplar (paricalcitol) capsules, NDA 21606 S-16, 17. Jane Liedtka, M.D. September 9, 2016, DARRTS Reference ID 3985667.

Consult Question: Please review new PLLR labeling being included in the label.

INTRODUCTION

On January 9, 2017, DMEP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of doxercalciferol injection labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On November 30, 2016, Hospira Inc. submitted a new drug application (NDA) via the 505 B (2) pathway for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis.
- The reference listed drug (RLD) for this product is NDA 021027 for Hectorol (doxercalciferol) Injection, 2 mcg/mL approved on April 6, 2000 for the treatment of secondary hyperparathyroidism in patients with CKD on dialysis.
- On January 23, 2017, the Agency sent the Applicant an Information Request requesting that they submit a literature search and a review and summary of the Applicant's pharmacovigilance database regarding doxercalciferol injection use in pregnant and lactating women and effects on fertility.
- On March 31, 2017, the Applicant submitted the requested supporting information which appeared adequate.

BACKGROUND

Hyperparathyroidism secondary to CKD[1]

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin as vitamin D3 and from dietary intake as either vitamin D2 or D3. Both vitamin D2 and D3 require two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [1,25(OH)2D3], is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. VDR activation is essential for the proper formation and maintenance of normal bone. In the diseased kidney, the activation of vitamin D is diminished, resulting in a rise of PTH, subsequently leading to secondary hyperparathyroidism and disturbances in the calcium and phosphorus homeostasis. Decreased levels of 1, 25(OH) 2D3 have been observed in early stages of chronic kidney disease. The decreased levels of 1, 25(OH) 2D3 and resultant elevated PTH levels, both of

[1] Zemplar 2014 package insert

which often precede abnormalities in serum calcium and phosphorus, affect bone turnover rate and may result in renal osteodystrophy.

Doxercalciferol and Drug Characteristics[2]

- A synthetic vitamin D2 analog that undergoes metabolic activation *in vivo* to form 1α,25-dihydroxy vitamin D2 (1α, 25-(OH)2D2), a naturally occurring, biologically active form of vitamin D2
- Molecular weight ≈ 413 Daltons
- Each milliliter (mL) of solution contains ethanol, (b) (4) mL
- Doxercalciferol is 99% protein bound.[3]
- Calcitriol (1α, 25-(OH) 2D3) and 1α, 25-(OH)2D2 regulate blood calcium at levels required for essential body functions. Specifically, the biologically active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction with parathyroid hormone (PTH), the mobilization of calcium from the skeleton.
- In uremic patients, deficient production of biologically active vitamin D metabolites (due to lack of or insufficient 25-hydroxyvitamin D-1-alpha-hydroxylase activity) leads to secondary hyperparathyroidism, which contributes to the development of metabolic bone disease in patients with renal failure.
- The mean elimination half-life of 1α, 25-(OH) 2D2 after an oral dose is ≈ 32 to 37 hours with a range of up to 96 hours.
- Most common adverse reactions (incidence > 10%) seen in clinical trials: edema, headache, malaise, nausea/vomiting, dyspnea and dizziness

Chronic Kidney Disease and Pregnancy

- CKD may affect up to 3% of females of reproductive potential.[4]
- Women with CKD or End Stage Renal disease (ESRD) have low fertility, due to altered levels of human chorionic gonadotropin (HCG) and reduced renal leptin clearance, anovulatory cycles, and hyperprolactinemia leading to oligomenorrhoea.[5]
- Pregnancy in the context of CKD carries a substantial increase in the risk of important obstetric and perinatal complications.[6]
- Maternal complications include cervical incompetence[7], spontaneous abortion/ miscarriage (24-29%)[8], preterm labor (71% with a mean estimated gestational age (EGA)

[2] Hectorol (doxercalciferol) Injection, 2 mcg/mL 2016 package insert
[3] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 354.
[4] Fitzpatrick A et al. Managing Pregnancy in chronic kidney disease: improving outcomes for mother and baby. Int J Womens Health. 2016; 8: 273-285.
[5] Swaroop R et al. Pregnancy in end stage renal disease patients on hemodialysis: Two case reports. Cases J. 2009; 2:8139.
[6] Tong A et al. Perspectives on pregnancy in women with chronic kidney disease: systematic review of qualitative studies. Nephrol Dial Transplant (2015) 30: 652–661.
[7] Pipili C et al. Pregnancy in dialysis-dependent women—the importance of frequent dialysis and collaborative care: A case report. Hemodialysis International 2011; 15:306–311.
[8] Jesudason S et al. Pregnancy Outcomes According to Dialysis Commencing Before or After Conception in Women with ESRD. Clin J Am Soc Nephrol. 2014; 9: 143–149.

of ≈ 33 weeks)[9], hypertension, pre-eclampsia and an increased incidence of delivery by caesarian section (37%).[10]

- Fetal complications include intrauterine growth retardation (IUGR), prematurity, polyhydramnios and stillbirth.[11] Infants usually have low birth weight (1511 ± 284 gm) and experience long stays in the neonatal intensive care unit [(NICU), 7-95 days].[12]
- Pediatric evaluation of children born to dialysis patients followed up for a period ranging between 2.5 and 5.5 years, showed a good long-term outcome. [13] Of importance to note is that infant malformations and maternal mortality are in line with the risk in the general population.[8]
- Significant improvement in the success rate for pregnancies reported among women with CKD on hemodialysis
    - advances in dialysis technique and maternal-fetal care
    - increased duration and frequency of HD sessions
    - supplementation of erythropoietin, iron, folate, and vitamins
    - adequate maternal nutrition
    - effective pharmaceutical support
    - close obstetric monitoring
    - advances in neonatal care.[3, 5]
        - 1980 the successful outcome rate (live births per pregnancy) was 23%,
        - 1998 this increased to 50%
        - During the last decade reached 81.3%.[7, 14, 15]

Current State of the Labeling for the RLD

Current labeling for Hectorol (doxercalciferol) Injection, 2 mcg/mL, approved on June 1, 2016, is in the non-PLRformat. There is no boxed warning, but there are Warnings for the following:

- Progressive hypercalcemia due to overdosage of vitamin D and its metabolites
- Exacerbation of tendencies for cardiac arrhythmias and seizures
- Potentiation of the action of digitalis drugs
- Generalized vascular calcification and other soft-tissue calcification
- Uncontrolled serum phosphorus exacerbates secondary hyperparathyroidism
- Interaction with magnesium-containing antacids
- Serious hypersensitivity reactions, including anaphylaxis

[9] Luders C et al. Obstetric outcome in pregnant women on long-term dialysis: a case series. Am J Kidney Dis 2010; 56:77–85.
[10]Yang LY et al. Obstetric outcomes in women with end-stage renal disease on chronic dialysis: A review. Obstr Med. 2010; 3:48–53.
[11] Bagon JA et al. Pregnancy and dialysis. Am J Kidney Dis. 1998; 31:756–765.
[12] Tan LK et al. Obstetric outcome in women with end stage renal failure requiring renal dialysis. Int J Gynaecol Obstet. 2006; 94:17–22.
[13] Moranne O et al. Pregnancy and hemodialysis. Nephrologie. 2004; 25:287–292.
[14] Successful pregnancies in women treated by dialysis and kidney transplantation: Report from the registration committee of the European Dialysis and Transplant Association. Br J Obstet Gynaecol. 1980; 87:839–845.
[15]Piccoli GB et al. Pregnancy in dialysis patients: Is the evidence strong enough to lead us to change our counseling policy? Clin J Am Soc Nephrol. 2010; 5:62–71.

Doxercalciferol is currently labeled as a Pregnancy Category B drug The **Use in Pregnancy** section for Hectorol states ". There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed".

The **Nursing Mothers** section for Hectorol states "It is not known whether doxercalciferol is excreted in human milk. Because other vitamin D derivatives are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from doxercalciferol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother".

No interactions with hormonal contraceptives are noted in the 2016 label.

REVIEW

Pregnancy

Nonclinical Experience

According to the applicant, reproduction studies in rats and rabbits, at doses up to 20 mcg/kg/day and 0.1 mcg/kg/day (approximately 25 times and less than the maximum recommended human oral dose of 60 mcg/week based on mcg/m2 body surface area, respectively) have revealed no teratogenic or fetotoxic effects due to doxercalciferol.

For further details, the reader is directed to the Nonclinical Review by Lee Elmore, PhD.

Applicant's Review of Literature

According to the Applicant, a cumulative search through to 30 January 2017 for doxercalciferol clinical studies was performed in the following databases: LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase. The search time frame was from 1946 through 30 January 2017. No relevant articles were identified.

Pharmacovigilance Database Summary

A cumulative search of the Pfizer safety database through to 23 January 2017 was performed. The search retrieved no relevant cases describing doxercalciferol injection and pregnancy, lactation, male or female fertility.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "doxercalciferol and pregnancy," "doxercalciferol and pregnant women," "doxercalciferol and pregnancy and birth defects," "doxercalciferol and pregnancy and

congenital malformations," "doxercalciferol and pregnancy and stillbirth," "doxercalciferol and spontaneous abortion", "doxercalciferol and premature rupture of membranes" and "doxercalciferol and pregnancy and miscarriage." No reports of adequate and well-controlled studies of doxercalciferol use in pregnant women were found. No case reports were identified.

Doxercalciferol is not referenced in *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*[16].

Micromedex[17] notes that doxercalciferol has a rating of "category B" by the FDA and that "due to the lack of human safety information, doxercalciferol should only be given to pregnant women if use is clearly justified".[18]

Summary

There are no human pregnancy outcome data for doxercalciferol in the published literature. The findings in animal studies did not demonstrate any findings indicative of risk to the fetus. Based on the review of published literature in the earlier section of this review, entitled **Chronic Kidney Disease and Pregnancy**, DPMH recommends a "Clinical Considerations" subsection be added to subsection 8.1. See DPMH proposed labeling below for further details.

Lactation

Nonclinical Experience

There is no information from animal studies regarding doxercalciferol and lactation.

Applicant's Review of Literature

According to the Applicant, a cumulative search through to 30 January 2017 for doxercalciferol clinical studies was performed in the following databases: LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase. The search time frame was from 1946 through 30 January 2017. No relevant articles were identified.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*[19], the Drugs and Lactation Database (LactMed),[20] Micromedex[21], and of published literature in PubMed and Embase

[16] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[17] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/1/16.
[18] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/1/16.
[19] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.
[20] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk,

using the search terms “doxercalciferol and lactation” and “doxercalciferol and breastfeeding.” No reports of adequate and well-controlled studies of doxercalciferol use in lactating women were found.

In *Medications and Mother’s Milk*[14], Thomas Hale, a breastfeeding expert, states the following regarding paricalcitol use during lactation:

> No data. Probably compatible…It is not likely that normal doses would lead to clinically relevant levels in human milk, particularly since Vitamin D transfers only minimally into human milk.

Doxercalciferol is not referenced in LactMed.

Micromedex notes the following;

> Infant risk cannot be ruled out… Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

Doxercalciferol is not referenced in *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk.*[17]

Summary

There are no data on the presence of doxercalciferol in animal or human milk. Although paricalcitol has high protein binding, the drug has other characteristics, including molecular weight <800 Daltons and a long half-life in patients with CKD, which may increase the presence of the drug in maternal circulation and may increase transfer of the drug into breastmilk. However, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk. Given all of the unknowns and the potential for elevated calcium in the breastfed infant exposed to doxercalciferol, DPMH recommends a “Clinical Considerations” subsection be added to subsection 8.2. See DPMH proposed labeling below for further details.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

Long-term studies in animals to evaluate the carcinogenic potential of doxercalciferol have not been conducted. No evidence of genetic toxicity was observed in an *in vitro* bacterial mutagenicity assay (Ames test) or a mouse lymphoma gene mutation assay. Doxercalciferol

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infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[21] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/1/16.

caused structural chromatid and chromosome aberrations in an in vitro human lymphocyte clastogenicity assay with metabolic activation. However, doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity assay. Doxercalciferol had no effect on male or female fertility in rats at oral doses up to 2.5 mcg/kg/day (approximately 3 times the maximum recommended human oral dose of 60 mcg/wk based on mcg/m2 body surface area).

For further details, the reader is directed to the Nonclinical Review by Lee Elmore, PhD.

Applicant's Review of Literature

The Applicant did not conduct a review of the literature.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding doxercalciferol and its effects on fertility and found no relevant literature.

Summary

Animal reproductive studies of administration of doxercalciferol injection did not show any adverse effects on fertility. Since there are no human data available on the effect of doxercalciferol injection on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in doxercalciferol injection labeling.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for doxercalciferol injection labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of doxercalciferol injection labeling was structured in the PLLR format to include the "Risk Summary" "Data" and "Clinical Considerations".[22]
- **Lactation, Section 8.2**
  - The "Lactation" section of doxercalciferol injection was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" sections.[23]

[22] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[23] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

LABELING RECOMMENDATIONS

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

DPMH Proposed Doxercalciferol Injection Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 Use in Specific Populations
8.1 Pregnancy
Risk Summary
There are no human data with doxercalciferol injection in pregnant women to inform the drug-associated risk for adverse developmental outcomes. There are risks to the mother and fetus associated with chronic kidney disease in pregnancy *[see Clinical Considerations]*. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits administered doxercalciferol during organogenesis at approximately 25 times and less than the maximum recommended human oral dose of 60 mcg/week based on mcg/m^2 body surface area, respectively *[See Data]*.

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

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Chronic kidney disease in pregnancy increases the maternal risk for hypertension, spontaneous abortion, preterm labor, and preeclampsia. Chronic kidney disease increases the fetal risk for intrauterine growth restriction (IUGR), prematurity, polyhydramnios, still birth, and low birth weight.

Data
Animal Data
There were no adverse effects on fetal growth or survival at doses up to 20 mcg/kg/day, when doxercalciferol was administered to pregnant female rats during organogenesis. When administered to pregnant female rabbits during organogenesis, there were no adverse effects on fetal growth or survival at doses up to 0.3 mcg/kg/day.

8.2 Lactation
Risk Summary
There is no information available on the presence of doxercalciferol injection in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for doxercalciferol injection and any potential adverse effects on the breast-fed child from doxercalciferol injection or from the underlying maternal condition.

Clinical Considerations

Infants exposed to doxercalciferol injection through breast milk should be monitored for signs and symptoms of hypercalcemia, including seizures, vomiting, constipation and weight loss. Monitoring of serum calcium in the infant should be considered.

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/s/

JANE E LIEDTKA
08/22/2017

MIRIAM C DINATALE
08/22/2017

LYNNE P YAO
08/23/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	August 7, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208614
Product Name and Strength:	doxercalciferol injection 2 mcg/mL
Total Product Strength:	4 mcg/2 mL and 10 mcg/5 mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira Inc.
Submission Date:	November 30, 2016
OSE RCM #:	2016-2746
DMEPA Primary Reviewer:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) consulted DMEPA to evaluate the proposed labels and labeling for doxercalciferol injection 2 mcg/mL, submitted by Hospira Inc. on November 30, 2016, under NDA 208614 utilizing the 505(b)(2) regulatory pathway. We reviewed the proposed labels and labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Hospira's submission for doxercalciferol injection under NDA 208614 proposes a 4 mcg/2 mL multi-dose vial, which is in alignment with the reference listed drug (RLD), and a new 10 mcg/5 mL multi-dose vial to provide additional dosing flexibility with less waste. The RLD is Hectorol, which was approved on April 6, 2000, under NDA 021027.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Hospira Inc. submitted a 505(b)(2) NDA for doxercalciferol injection, with Hectorol as the RLD. We performed a risk assessment of the container labels, carton labeling, and Prescribing Information to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed labeling that could be improved to promote the safe use of the product.

For the Division, we recommend defining the acronym "iPTH" and adding information regarding identifying characteristics to the DOSAGE FORMS AND STRENGTHS and HOW

SUPPLIED/STORAGE AND HANDLING sections. For added clarity, we restructured how the product information is displayed in Section 16 and recommend adding information regarding storage of opened multi-dose vials to mitigate any confusion.

For the Applicant, we suggest adding a discard after statement on the container labels for healthcare providers to write a post-opening expiration date on the label. In addition, we recommend assigning a non-sequential number for the NDC number and assigning different NDC package codes for different container and carton sizes. Finally, we recommend changing the usual dosage statement on the carton labeling, and displaying where the lot number and expiration date will be positioned on the carton.

4 CONCLUSION & RECOMMENDATIONS

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

4.1 RECOMMENDATIONS FOR THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION (HPI)
   a. DOSAGE AND ADMINISTRATION – Define the acronym "iPTH" the first time it appears in the HPI as follows: "...and based on intact parathyroid hormone (iPTH) levels with..."

B. PRESCRIBING INFORMATION (PI)
   a. Section 2 DOSAGE AND ADMINISTRATION, Section 2.1 Initial Dose and Titration – Define the acronym "iPTH" the first time it appears in the PI as follows: "...and based on intact parathyroid hormone (iPTH) levels with..."
   b. Section 3 DOSAGE FORMS AND STRENGTHS – Add information regarding identifying characteristics, and rephrase this section as follows:

      4 mcg/2 mL, as a clear, colorless aqueous solution in multi-dose vials
      10 mcg/5 mL, as a clear, colorless aqueous solution in multi-dose vials

   c. Section 16 HOW SUPPLIED/STORAGE AND HANDLING
      i. Add information regarding identifying characteristics, and rephrase the first sentence as follows: "Doxercalciferol injection is supplied as a clear, colorless aqueous solution in multi-dose amber glass vials ..."
      ii. For added clarity and to reduce confusion, remove the table and display product information as follows:

NDC 0409-1330-01	4 mcg/2 mL multi-dose vial	carton of 50 x 2 mL
NDC 0409-1331-01	10 mcg/5 mL multi-dose vial	carton of 50 x 5 mL

      iii. Add information on storage of opened Multi-dose Vials (i.e., Discard opened vials 14 days after initial use).

4.2 RECOMMENDATIONS FOR HOSPIRA INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container
   1. As currently presented, the middle digits for the National Drug Code (NDC) numbers are assigned in a sequential manner (e.g., 1330 and 1331). Avoid assigning product codes that are numerically similar or identical per Draft Guidance: Container and Carton, April 2013 (lines 521-544). The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type (e.g., 0409-**1330**-01 and 0409-**1331**-01).
   2. The container label of one unit and the carton labeling of 50 units should have different NDC numbers. Revise the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.
   3. If space permits consider adding a discard after statement for healthcare providers to write a post-opening expiration date on the label as follows: "Discard after ___ /___ /___"
      Adding a discard after statement in this format has shown to result in the desired action and alerts healthcare providers to write a complete date (e.g., month, day, and year) on the container label.

B. Carton
   1. See A.1.
   2. See A.2.
   3. Consider revising the usual dosage statement to read as follows: "See prescribing information"
   4. Display where the lot number and expiration date will be positioned on the carton in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively, as this is information is currently missing.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for doxercalciferol that Hospira Inc. submitted on November 30, 2016, and March 31, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for doxercalciferol and the Listed Drug

Product Name	**doxercalciferol**	**Hectorol**
Initial Approval Date	N/A	04/06/2000
Active Ingredient	doxercalciferol	doxercalciferol
Indication	treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis	
Route of Administration	intravenous	
Dosage Form	injection	
Strength	2 mcg/mL • 4 mcg/2 mL • 10 mcg/5 mL	2 mcg/mL (4 mcg/2 mL)
Dose and Frequency	individualized and based on iPTH levels with monitoring of serum calcium and serum phosphorus levels	
How Supplied	4 mcg/2 mL (2 mcg/mL) in a multi-	2 mcg/mL in a single-dose amber glass vial packaged as (b) (4) 4 mcg/2 mL (2 mcg/mL) in a single-dose amber glass vial packaged as (b) (4) 4 mcg/2 ml (2 mcg/mL) in a multi-

Initial Dose

iPTH Level	Doxercalciferol Injection Dose
>400 pg/mL	4 mcg three times per week at the end of dialysis, or approximately every other day

Dose Titration

iPTH Level	Doxercalciferol Injection Dose
Decrease by <50% and above 300 pg/mL	Increase by 1 to 2 mcg at eight-week intervals as necessary
Decrease by >50% and above 300pg/mL	Maintain
150 to 300 pg/mL	Maintain
<100 pg/mL	Suspend for one week, then resume at a dose that is at least 1 mcg lower

	dose amber glass vial packaged as 50 x 2 mL 10 mcg/5 mL (2 mcg/mL) in a multi-dose amber glass vial packaged as 50 x 5 mL	dose amber glass vial packaged as (b) (4)
Storage	unopened vial: 20° to 25°C (68° to 77°F) opened vial: 20° to 25°C (68° to 77°F), stable up to 14 days after first use protect from light	single-dose vial: 25°C (77°F), excursions permitted to 15–30°C (59–86°F), discard unused portion multi-dose vial • unopened: 25°C (77°F), excursions permitted to 15–30°C (59–86°F) • opened: 2–8°C (36–46°F), stable up to three days after first use protect from light
Container Closure	4 mcg/2 mL (2 mcg/mL) vials packaged in a carton containing 50 x 2 mL with a closure consisting of a fluorocarbon-coated chlorobutyl stopper, aluminum seal, and orange plastic flip-off cap 10 mcg/5 mL (2 mcg/mL) vials packaged in a carton containing 50 x 5 mL with a closure consisting of a fluorocarbon-coated chlorobutyl	2 mcg/mL single-dose vials packaged in a carton containing (b) (4) with a closure consisting of a fluorocarbon-coated chlorobutyl stopper, aluminum seal, and green plastic flip-off cap 4 mcg/2 mL (2 mcg/mL) single-dose vials containing (b) (4) with a closure consisting of a fluorocarbon-coated chlorobutyl stopper, aluminum seal, and yellow plastic flip-off cap 4 mcg/2 mL (2 mcg/mL) multi-dose vials packaged in a carton containing (b) (4) with a closure consisting of a fluorocarbon-coated chlorobutyl stopper, aluminum seal, and orange plastic flip-off cap

	stopper, aluminum seal, and gray plastic flip-off cap	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 19, 2017, we searched the L:drive and AIMS using the terms, Hectorol or doxercalciferol, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant for this review.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 19, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters 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 Edition, and Nursing Edition
Search Strategy and Terms	Boolean Query: Hectorol or doxercalciferol

D.2 Results

Our search identified one case, which was not relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following doxercalciferol labels and labeling submitted by Hospira Inc. on November 30, 2016, and March 31, 2017.

- Prescribing Information
- Container Labels
- Carton Labeling

G.2 Label and Labeling Images

Prescribing Information

Application 208614 - Sequence 0003 - Doxercalciferol USPI Hospira Track Changes LAB-0887-1.1 Apr 2017 [\\cdsesub1\evsprod\nda208614\0003\m1\us\lab-0887-1-1-pkg-insert-track.doc]

Container Labels

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

Carton Labeling

(b) (4)

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/s/

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08/07/2017

HINA S MEHTA
08/08/2017