CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMO

NDA	208-614 Serial 0006
Submission Date	January 26, 2018
Generic Name	Doxercalciferol
Brand Name	Unknown
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.*
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Hospira Inc.
Formulation; Strength	Intravenous injection; 4 µg/2 mL and 10 µg/5 mL
Indication	Treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on dialysis

This memo documents the rationale for the major Clinical Pharmacology recommendations and comments for the review of doxercalciferol injection label.

Notes on Labeling Recommendation

The approved HECTORL injection label (NDA 21-027; innovator product) is the basis for this proposed label of doxercalciferol injection in NDA 208-614. This reviewer also recommended changes to the proposed doxercalciferol injection label according to the following approved labels of other vitamin D products to maintain consistency among these product labels:

- ZEMPLAR (NDA 021-606; paricalcitol capsule PLR label)
- CALCIJECT (NDA 018-874; calcitriol injection label)
- ROCALTROL (NDA 021-068; calcitriol oral solution label)

Recommendations	Comments
7 DRUG INTERACTIONS **Drugs that May Increase the risk of Hypercalcemia** **Clinical Impact** Concomitant administration of high doses of calcium containing preparations or other vitamin D compounds may increase the risk of hypercalcemia. Thiazide diuretics are known to induce hypercalcemia by reducing excretion of calcium in the urine. **Examples** Calcium containing products, other vitamin D compounds or thiazide diuretics **Intervention** Monitor serum calcium concentrations more frequently and adjust Doxercalciferol Injection dose as needed [see Warnings and Precautions (5.1)].	Hypercalcemia can result from significant drug interaction between doxercalciferol and other drugs.
7 DRUG INTERACTIONS **Digitalis Compounds** **Clinical Impact** Doxercalciferol Injection can cause hypercalcemia which can potentiate the risk of digitalis toxicity. **Intervention** Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium	Digitalis toxicity is potentiated by hypercalcemia.

monitoring when initiating or adjusting the dose of Doxercalciferol Injection in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].	
7 DRUG INTERACTIONS **Cytochrome P450 Inhibitors** **Clinical Impact** Doxercalciferol is activated by CYP 27 in the liver. Cytochrome P450 inhibitors may inhibit the 25-hydroxtlation of doxercalciferol and thus reduce the formation of active doxercalciferol moiety [see Clinical Pharmacology (12.3)]. **Examples** Ketoconazole and erythromycin **Intervention** If a patient initiates or discontinues therapy with a cytochrome P450 inhibitor, dose adjustment of Doxercalciferol Injection may be necessary. Monitor intact PTH and serum calcium concentrations closely.	Doxercalciferol needs metabolic activation by CYP 27. Thus, CYP inhibitors can hinder the formation of active doxercalciferol metabolite. The example inhibitors are not CYP 27 specific. Thus, this reviewer recommends using "Cytochrome P450 Inhibitors."
7 DRUG INTERACTIONS **Enzyme Inducers** **Clinical Impact** Doxercalciferol is activated by CYP 27 in the liver. Enzyme inducers may affect the 25-hydroxylation of doxercalciferol [see Clinical Pharmacology (12.3)]. **Examples** Glutethimide and phenobarbital **Intervention** If a patient initiates or discontinues therapy with an enzyme inducer, dose adjustment of Doxercalciferol Injection may be necessary. Monitor intact PTH and serum calcium concentrations closely.	Doxercalciferol needs metabolic activation by CYP 27. Because the example inducers are not specific for CYP enzymes. Thus, this reviewer recommends using "Enzyme Inducers."
7 DRUG INTERACTIONS **Magnesium Containing Products** **Clinical Impact** Concomitant administration of Doxercalciferol Injection and high doses of magnesium containing products may increase the risk of hypermagnesemia. **Examples** Magnesium containing products such as antacids Intervention Monitor serum magnesium concentrations more frequently and adjust Doxercalciferol Injection dose as needed.	The risk of hypermagnesemia is due to excess magnesium intake and large dose of vitamin D (Kanis et al. *BMJ* 1976; Spencer et al. *Gastroenterology* 1980).

(b) (4)

12.1 Mechanism of Action Doxercalciferol is a synthetic vitamin D_2 analog that requires metabolic activation to form the active 1α,25-$(OH)_2D_2$ metabolite, which binds to the vitamin D receptor (VDR) to result in the selective activation of vitamin D responsive pathways. Vitamin D and doxercalciferol have been shown to reduce parathyroid hormone (PTH) levels by inhibiting PTH synthesis and secretion	This reviewer rewrites Section 12.1 to be consistent with that of other vitamin D products' label.
12.3 Pharmacokinetics <u>Elimination</u> The mean elimination half-life of 1α,25-$(OH)_2D_2$ after an oral dose is approximately 32 to 37 hours with a range of up to 96 hours. The mean elimination half-life in patients with end stage renal disease (ESRD) and in healthy volunteers appears to be similar following an oral dose. Doxercalciferol Injection is not approved for oral use. Hemodialysis causes a temporary increase in 1α,25-$(OH)_2D_2$ mean concentrations presumably due to volume contraction. 1α,25-$(OH)_2D_2$ is not removed from blood during hemodialysis.	The review team asked the sponsor to provide mean elimination half-life of 1α,25-$(OH)_2D_2$ (active metabolite) after IV injection for this doxercalciferol injection label because the proposed language is for oral administration. However, NDA 208-614 is a 505(b)(2) NDA; this sponsor does not have access to the innovator product's data. The review team considered to delete the statements that pertain to oral dose of doxercalciferol but decided not to delete. While the innovator label didn't have the half-life of the active metabolite after IV administration, the terminal half-life of active metabolite is not expected to be different between IV and oral routes of administration because the elimination half-life of the active metabolite is mostly driven by the intrinsic property of the body. The half-life information for the active metabolite would still be informative for prescribers to make decisions such as length of washout period and time to steady state. Thus, the review team recommends keeping this information.
12.3 Pharmacokinetics *Metabolism* After intravenous administration, doxercalciferol is activated by CYP 27 in the liver to form 1α,25-$(OH)_2D_2$ (major metabolite) and 1α,24-dihydroxyvitamin D_2 (minor metabolite). Activation of doxercalciferol does not require the involvement of the kidneys.	Directly from the HECTOROL injection label.

* Dr. Manoj Khurana helped review the proposed labeling language for Section 12.3 as the acting Team Leader while Dr. Jayabharathi Vaidyanathan was on leave.

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/s/

SZE W LAU
07/19/2018

MANOJ KHURANA
07/19/2018