# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211379Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Office of Clinical Pharmacology Review

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| **NDA Number (SDN)** | 211379 (1, 10) |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA211379\211379.enx |
| **Submission Date** | September 6, 2018; June 21, 2019 |
| **Submission Type** | Standard |
| **Brand Name** | HEMADY |
| **Generic Name** | Dexamethasone |
| **Dosage Form and Strength** | Tablet, 20 mg |
| **Route of Administration** | Oral |
| **Proposed Indication** | In combination regimens with anti-myeloma drugs for the treatment of patients with multiple myeloma (MM) |
| **Applicant** | Dexcel Pharmaceutics |
| **Associated Applications** | NDA 011664 [Decadron (dexamethasone); Merck],<br>NDA 020785 [Thalomid (thalidomide); Celgene],<br>NDA 021602 [Velcade (bortezomib); Millennium],<br>NDA 021880 [Revlimid (lenalidomide); Celgene],<br>NDA 204026 [Pomalyst (pomalidomide); Celgene],<br>NDA 205353 (Farydak (panobinostat); Novartis],<br>NDA 208462 [Ninlaro® (ixazomib); Millennium], and<br>NDA 202714 [Kyprolis (carfilzomib); Onyx Pharmaceuticals] |
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## Tables and Figures

# 1. EXECUTIVE SUMMARY

Dexcel Pharma submitted a 505(b)(2) NDA to seek approval for HEMADY, a higher strength of dexamethasone tablet, 20 mg, for the treatment of patients with multiple myeloma (MM) in combination regimens with anti-myeloma drugs. The application cross-references the following listed drugs:

i. Decadron (dexamethasone) Tablets 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg (NDA 011664, Merck, approved October 30, 1958, discontinued),
ii. Thalomid (thalidomide) Capsules (NDA 020785, Celgene),
iii. Velcade (bortezomib) Injection (NDA 021602, Millennium Pharmaceuticals, Inc.),
iv. Revlimid (lenalidomide, NDA 021880, Celgene),
v. Pomalyst (pomalidomide, NDA 204026, Celgene),
vi. Farydak (panobinostat, NDA 205353, Novartis Pharmaceuticals Corporation),
vii. Ninlaro® (ixazomib, NDA 208462, Millennium Pharmaceuticals, Inc.), and
viii. Kyprolis (carfilzomib, NDA 202714).

HEMADY will not be indicated for the indications listed in the Decadron labeling.

Decadron was withdrawn in 2007. Several generic versions of Decadron Tablets are currently approved including, West-Ward's Dexamethasone Tablets, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg and 6 mg (ANDAs 084611 084613, 084610, 087916, 084612, 088306, & 088316).

Dexcel Pharma conducted a clinical pharmacology study in healthy subjects to compare bioavailability of the proposed HEMADY 20 mg tablet to the marketed tablet formulation, and to determine effect of food on the bioavailability of HEMADY (Study 160458). Since Decadron has been discontinued, West-Ward Pharmaceuticals' 4 mg dexamethasone (ANDA 084612) tablet was used in the study. The Applicant did not conduct any other clinical studies.

The key review questions focused on establishment of a scientific bridge between the proposed HEMADY 20 mg tablet and Decadron, demonstration of dose-PK linearity within the proposed dose range, and the appropriateness of dose recommendations for the HEMADY labeling that is based on the Decadron labeling and applicable for this indicated patient population.

## 1.1 Recommendations

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA.

| Review | Recommendations and Comments |
|---|---|
| Supportive evidence of effectiveness | Based on the clinical studies of dexamethasone in combination with other anti-myeloma drugs, provided in the prescribing information for each of the other listed anti-myeloma drugs. |
| General dosing instructions | Oral dose of 20 mg or 40 mg daily on specific days of treatment cycle in combination with the other listed anti-myeloma drugs. The dosing regimen of HEMADY will be specified in the prescribing information of each of the listed anti-myeloma drugs. HEMADY can be taken with or without food. |

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| Dosing in patient subgroups (intrinsic and extrinsic factors) | • No dose adjustment with food based on Study 160458.<br><br>The following recommendations are based on the labeling for Decadron and literature:<br><br>• Avoid coadministration of strong CYP3A4 modulators or consider alternative medication with minimal or no inhibition or induction of CYP3A4. If concomitant use of strong CYP3A4 inhibitors cannot be avoided, closely monitor for adverse drug reactions. If concomitant use strong CYP3A4 inducers cannot be avoided, consider increasing the dose of HEMADY.<br>• Avoid coadministration of cholestyramine and HEMADY and consider alternative agents.<br>• Consider increasing the dose of HEMADY when used concomitantly with ephedrine.<br>• Closely monitor potassium levels when coadministered with potassium-depleting agents (e.g., amphotericin B, diuretics).<br>• Monitor for toxicity when aspirin is coadministered with HEMADY in hypoprothrombinemia.<br>• Frequently monitor coagulation indices to maintain desired coagulation effect when coadministered with HEMADY.<br>• Consider dose adjustment of antidiabetic drugs when coadministered with HEMADY.<br>• Monitor for risk of thromboembolism in patients with MM receiving anti-myeloma products with HEMADY.<br>• Closely monitor for toxicity when thalidomide is coadministered with HEMADY.<br>• If possible, defer routine administration of vaccines or toxoids until HEMADY therapy is discontinued.<br>• Monitor for toxicity in patients with hepatic impairment HI.<br>• No dose adjustment for patients with MM and any renal impairment (RI).<br>• No dose adjustments for thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib or carfilzomib when coadministered with HEMADY.<br>• No dose adjustment of HEMADY when coadministered with thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib or carfilzomib. |
| Bridge between the "to-be-marketed" and listed drug formulations | Bioequivalence between HEMADY, 20 mg tablet and approved West-Ward's Dexamethasone 4 mg tablet was demonstrated. In addition, PK linearity within the proposed dose range was demonstrated. Therefore, a scientific bridge exists between DECADRON and HEMADY tablet and dexamethasone oral products in literature to support the labeling recommendations. |

## 1.2 Post-Marketing Requirements and Commitment

None.

# 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1 Pharmacology and Clinical Pharmacokinetics

Dexamethasone is a synthetic glucocorticoid. Glucocorticoids cause varied metabolic effects and modify the body's immune responses to diverse stimuli. The following is a summary of the clinical pharmacokinetics (PK) of dexamethasone. The following PK parameters are from Study 160458, Decadron labeling, or literature (Appendix 4.4, 4.2, and Error! Reference source not found.). The metabolism and excretion data are from the current Decadron labeling and literature. Information from Study 160458, Decadron labeling, and literature are identified where applicable:

Absorption: The absolute bioavailability of HEMADY 20 mg tablet has not been evaluated. The bioavailability of oral dexamethasone formulations based on literature data is between 60 to 80% at formulation strengths between 0.5 mg and 100 mg. The median $T_{max}$ of HEMADY 20 mg was ~ 1 hour. Literature data suggests that the PK of dexamethasone was dose proportional between 0.5 mg to 300 mg of oral dexamethasone formulations.

Effect of Food: High-fat meal did not affect the exposure (AUC) of dexamethasone, but decreased Cmax by 30%, and delayed median Tmax by 1.5 hours following administration of 20 mg of HEMADY tablet.

Distribution: Literature data suggests protein binding is ~75 to 77%, mainly to albumin.

Metabolism: Literature data suggests dexamethasone is primarily cleared via the hepatic route. Renal clearance is <10% of the total body clearance. Dexamethasone undergoes hepatic metabolism. Dexamethasone is metabolized by CYP3A4 per Decadron labeling. Literature data suggests 6ß-hydroxydexamethasone as the major metabolite.

Elimination: The mean elimination half-life was about 4 hours. The clearance (CL/F) of HEMADY tablet was 15 L/hr at 20 mg in subjects, which is within the range reported in the literature. The CL/F values in the literature ranged from 7.75 L/hr to 44.5. L/h at oral doses between 0.5 to 300 mg.

Excretion: 10% of the dose excreted as unchanged.

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General dosing*

Oral HEMADY dose of 20 mg or 40 mg daily in combination with the other listed anti-myeloma drugs on specific days of treatment cycle depending on the treatment regimen as specified in the prescribing information of the other listed anti-myeloma drugs. The dosing regimen of HEMADY in combination with the other listed anti-myeloma drugs are based on the efficacy and safety data in the clinical studies described in the prescribing information for each of the other listed anti-myeloma drugs (see Table 1).

Table 1: Dexamethasone Dosing Regimen for the Other Listed Anti-Myeloma Drugs

| *Drug Labeling* | Dexamethasone Dosing Regimen for Multiple Myeloma (MM) |
|---|---|
| *Thalomid (thalidomide) NDA 020785* | MM, Td: 40 mg/day on days 1-4, 9-12, and 17-20 every 28 days |

| | |
|---|---|
| *Velcade (bortezomib) NDA 021602* | Relapsed MM, Vd: After four cycles, 20 mg orally daily on the day of and after VELCADE administration<br>Retreatment of Relapsed MM, Vd: With VELCADE in Cycle 1, with an additional 11 patients receiving dexamethasone during the course of VELCADE retreatment cycles |
| *Revlimid (lenalidomide) NDA 21880* | MM, Rd Continuous and Rd18 arms (25 mg R QD D1-21): 40 mg (20 mg > 75 years) once daily on Days 1, 8, 15, and 22 of each 28-day cycle<br>MM with **≥1** therapy, Rd (25 mg R QD D1-21): 40 mg orally QD on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles and 40 mg orally QD on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. |
| *Pomalyst (pomalidomide) NDA 204026* | MM, Pd:<br>Low-dose: 40 mg (20 mg if >75 years) daily on Days 1, 8, 15, and 22 of each 28-day cycle<br>High-dose: 40 mg (20 mg if >75 years) daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle |
| *Ninlaro (ixazomib) NDA 208462* | NRd: 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle |
| *Farydak (panobinostat) NDA 205353* | FVd (C1-8): 20 mg orally 1, 2, 4, 5, 8, 9, 11, 12 of 21-day cycle on a full stomach<br>FVd (C9-16): 20 mg orally 1, 2, 8, 9 of 21-day cycle on a full stomach |
| *Kyprolis (carfilzomib) NDA 202714* | Kd 20/70: 40 mg orally or IV on Days 1, 8, and 15 of all cycles and on Day 22 of Cycles 1 to 9<br>Kd 20/56: 20 mg orally or IV on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle<br>KRd 20/27: 40 mg by orally or IV on Days 1, 8, 15, and 22 of the 28-day cycles |

d=dexamethasone, T=Thalomid, V=Velcade, R=Revlimid, P=Pomalyst, N=Ninlaro, F=Faydak, K=Kyprolis
Source: Based on Thalomid, Velcade, Revlimid, Pomalyst, Ninlaro, Faydak, and Kyprolis labeling

### *2.2.2 Therapeutic individualization*

- Avoid coadministration of strong CYP3A4 modulators or consider alternate medication with minimal or no inhibition or induction of CYP3A4. If concomitant use strong CYP3A4 inhibitors cannot be avoided, closely monitor for adverse drug reactions. If concomitant use strong CYP3A4 inducers cannot be avoided, consider increasing the dose of HEMADY.
- Avoid coadministration of cholestyramine and HEMADY and consider alternative agents.
- Consider increasing the dose of HEMADY when used concomitantly with ephedrine.
- Closely monitor potassium levels when coadministered with potassium-depleting agents (e.g., amphotericin B, diuretics).
- Monitor for toxicity when aspirin is coadministered with HEMADY in hypoprothrombinemia.
- Frequently monitor coagulation indices to maintain desired coagulation effect when coadministered with HEMADY.
- Consider dose adjustment of antidiabetic drugs when coadministered with HEMADY
- Monitor for risk of thromboembolism in patients with MM receiving anti-myeloma products with HEMADY.
- Closely monitor for toxicity when thalidomide is coadministered with HEMADY.
- The effect of baseline hepatic or renal impairment on PK of dexamethasone has not been evaluated.
- If possible, defer routine administration of vaccines or toxoids until HEMADY therapy is discontinued
- No dose adjustment for patients with MM and any RI.
- No dose adjustments for thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib

or carfilzomib when coadministered with HEMADY.

- No dose adjustment of HEMADY when coadministered with thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib or carfilzomib.

### 2.3 Outstanding Issues

No outstanding issues.

## 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

### 3.1 Overview of the Product and Regulatory Background

Decadron Tablets 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg, and 6 mg, were approved on October 30, 1958 (NDA 011664, Merck). Decadron was approved for multiple indications, including allergic states, multiple disorders (endocrine, gastrointestinal, rheumatic) and diseases (ophthalmic, respiratory, dermatologic, nervous system, renal) and palliative management of leukemias and lymphomas[1]. The recommended initial oral doses of Decadron ranged between 0.75 and 9 mg daily depending upon disease type, and 30 mg daily dose for a week followed by 4 to 12 mg every other day for a month for the treatment of acute exacerbations of multiple sclerosis[1]. Decadron was withdrawn from the market in 2007. Several generic versions of Decadron Tablets are currently approved including, West-Ward's Dexamethasone Tablets, 0.5 mg (ANDA 084611), 0.75 mg (ANDA 084613), and 1.5 mg (ANDA 084610) approved between May and July 1975, 2 mg (ANDA 087916) approved on August 26, 1982, 4 mg (ANDA 084612) approved on July 19, 1978, 1 mg (ANDA 088306) and 6 mg (ANDA 088316) approved on September 15, 1983.

In the current NDA, the Applicant is seeking approval for a higher strength of dexamethasone tablet via the 505(b)(2) approval pathway. The Applicant proposes HEMADY (dexamethasone) 20 mg Tablet, for the treatment of patients with multiple myeloma (MM) in combination regimens with anti-myeloma drugs. HEMADY will not be indicated for the indications listed in the Decadron labeling. In addition to Decadron, the Applicant cross-references FDA's finding of safety and/or effectiveness on listed anti-myeloma drugs: i) Thalomid (thalidomide) Capsules (NDA 020785, Celgene, approved July 16, 1998) and ii) Velcade (bortezomib) Injection (NDA 021602, Millennium Pharmaceuticals, Inc., approved May 13, 2003), iii) Revlimid (lenalidomide, NDA 021880, Celgene, approved December 27, 2005), iv) Pomalyst (pomalidomide, NDA 204026, Celgene, approved February 8, 2013), v) Farydak (panobinostat, NDA 205353, Novartis Pharmaceuticals Corporation, approved February 23, 2015), vi) Ninlaro® (ixazomib, NDA 208462, Millennium Pharmaceuticals, Inc., approved November 20, 2015), and vii) Kyprolis (carfilzomib, NDA 202714, Onyx Pharmaceuticals, Inc., approved July 20, 2012).

The Applicant proposes a HEMADY dose of 20 mg or 40 mg in combination with other listed anti-myeloma drugs depending on the treatment regimen as specified in the prescribing information of the other listed anti-myeloma drugs. These doses were based on effectiveness and safety of clinical studies that used dexamethasone in combination with anti-myeloma drugs, as described in the listed drug labeling.

[1] Decadron labeling dated May 2019. Drugs@FDA.

## 3.2 General Pharmacological and Pharmacokinetic Characteristics

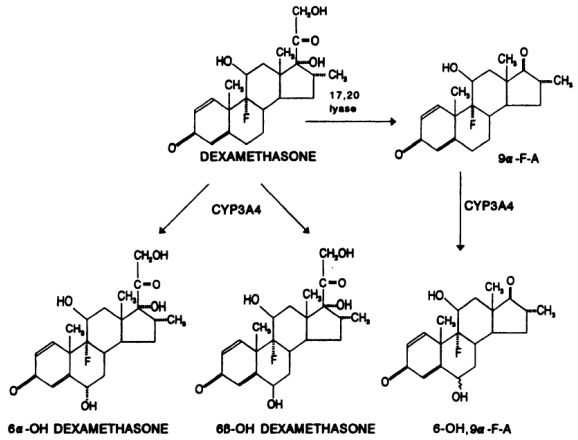
The PK parameters listed in Table 2 are from Study 160458 and literature (Appendix 4.2).

Table 2: Dexamethasone PK parameters

| | |
|---|---|
| **Pharmacology** | |
| Mechanism of Action | Glucocorticoids cause varied metabolic effects, and can modify the body's immune responses to diverse stimuli. |
| Active Moieties | Dexamethasone is metabolized by CYP3A4 per Decadron labeling. Literature data suggests 6ß-hydroxydexamethasone as the major metabolite. |
| QT Prolongation | No major QT prolongation issues reported in literature. |
| **General Information** | |
| Bioanalysis | Measured by LC/MS/MS following protein precipitation. |
| Healthy Volunteers vs. Patients | CL/F (%CV) of 15 L/hr (44%) in patients (n=4) and 19.5 L/hr (48%) in HV (n=24) following administration of oral formulations based on literature data |
| Drug exposure at single dose following the therapeutic dosing regimen | With 20 mg HEMADY (% CV) in 34 subjects:<br>$AUC_{0\text{-}inf}$: 1271 (31) ng*hr/mL.<br>$C_{max}$: 247 (31) ng/mL |
| Dose Proportionality | 0.5 to 300 mg based on literature data. |
| Accumulation | No significant accumulation with daily dosing. Racc of 07 – 0.8 based on daily dosing in literature. |
| Variability | 20-50% |
| **Absorption** | |
| Bioavailability [oral] | Bioavailability of HEMADY, 20 mg was not evaluated. Bioavailability of dexamethasone tablets in literature was between 60-80%. |
| $T_{max}$ | Median $T_{max}$: 1-2 hour |
| **Distribution** | |
| Plasma Protein Binding | 75-77% |
| **Elimination** | |
| Mean Terminal Elimination half-life | ~ 4 hours (18%) in subjects with 20 mg HEMADY tablets |
| Metabolism (Appendix 4.2) | |
| Primary metabolic pathway [*in vitro*] | Dexamethasone is metabolized by CYP3A per Decadron labeling. 6ß-Hydroxydexamethasone was the major metabolite. See Figure 1. |
| Inhibitor/Inducer | Decadron labeling and clinical studies in literature suggests that moderate to strong CYP3A4 inhibitors decrease and CYP3A inducers enhance the metabolism of dexamethasone. |
| Excretion (Appendix 4.2) | |
| Primary excretion Pathways (% dose) | Primarily cleared by the hepatic route. Renal CL was <10% of total body clearance based on literature. Less than 10% unchanged drug in urine. |

Metabolic Pathway of Dexamethasone:

Figure 1: Metabolic Pathway of Dexamethasone




9α-F-A= 9a-fluoro-androsta-1 ,4-diene-11 13-hydroxy-16a-methyl-3,17-dione; 6α-OH dexamethasone = 6α-hydroxydexamethasone, 6α-OH dexamethasone = 6ß-hydroxydexamethasone
*Source: Gentile et al. (1996). J. Pharmacol. Exp. Ther.; 277: 105-112.*

Dexamethasone is metabolized by CYP3A4. There were two 6-hydroxylation products: the major metabolite, 6ß-hydroxy-dexamethasone, and a relatively minor metabolite with 6a-hydroxydexamethaaone. Dexamethasone also underdoes side-chain cleavage to 9a-F-A. This metabolite was subsequently a substrate for 6-hydroxylation.[2]

## 3.3 Clinical Pharmacology Questions

### *3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?*

No. The dexamethasone dose of 20 mg or 40 mg daily in combination with the other listed anti-myeloma drugs are based on the efficacy and safety demonstrated in the clinical studies as described in the drug labeling for the listed anti-myeloma drugs. Also, refer to Section 3.3.2 for establishment of a scientific bridge.

### *3.3.2 Has a scientific bridge has been established between drug product(s) used in the literature studies and the proposed drug product to support the acceptance of the scientific literature?*

Yes. A scientific bridge has been established between the listed drug (i.e., Decadron) and HEMADY tablet, and the dexamethasone drug products used in the literature to support the labeling recommendations.

Study 160458 demonstrated that the bioavailability of HEMADY tablet, 1 x 20 mg is comparable to the West-Ward's Dexamethasone tablet, 5 x 4 mg, in that the 90% confidence intervals (CI) of the geometric mean ratio (GMR) for primary PK parameters, $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were within bioequivalence limits of 80% to 125% (Table 3: refer to Appendix 4.1 for details). In addition, the 90% CI of GMR of $AUC_{0-t}$, and $AUC_{0-\infty}$ of HEMADY tablet, 1 x 20 mg with a high-fat

[2]Gentile et al. (1996). *J. Pharmacol. Exp. Ther.*; 277: 105-112.

meal and under fasted conditions were also within bioequivalence limits (Table 3). The 23% decrease in Cmax with a high fat meal is not considered clinically significant. Therefore, the study results indicate no effect of food on the exposure of HEMADY tablet, 20 mg (refer to Appendix 4.1 for details), supporting the labeling recommendation to take HEMADY with or without food.

Table 3: Summary bioequivalence statistics for Study 160458

| Parameter (unit) | Ratio of Test / Reference | 90% Confidence Interval of Ratio |
|---|---|---|
| HEMADY 1x20 mg Tablet vs. West-Ward's 5 x 4 mg Tablet | | |
| $AUC_{0-t}$ (h*ng/mL) | 99.4 | 95.66 – 103.22 |
| $AUC_{0-\infty}$ (h*ng/mL) | 99.2 | 95.46 – 103.10 |
| Cmax (ng/mL) | 106.3 | 97.71 – 115.63 |
| HEMADY 1x20 mg Tablet, Fed vs. Fasted | | |
| $AUC_{0-t}$ (h*ng/mL) | 103.1 | 99.15 – 107.33 |
| $AUC_{0-\infty}$ (h*ng/mL) | 103.4 | 99.30 – 107.60 |
| Cmax (ng/mL) | 77.1 | 69.45 – 85.54 |

Dose proportionality

Investigation of dose proportionality of PK of dexamethasone after oral dosing based on literature data indicated linear relationships between dose and CL/F, Cmax, and AUC between 0.5 mg and 300 mg (refer to Appendix 4.2 for details).

### *3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?*

Yes. Monitor for toxicity in patients with hepatic impairment (HI). No dose adjustment for patients with any renal impairment (RI).

Hepatic impairment (HI):

No clinical studies have been conducted. Dexamethasone clearance was decreased and half-life was increased in patients with chronic liver disease (hepatic classification of patients was not provided, refer to Appendix 4.4). Therefore, patients with hepatic impairment should be monitored for signs and symptoms of toxicity following treatment with HEMADY.

Renal Impairment (RI):

No dose adjustment is necessary for patients with MM and any renal impairment receiving anti-myeloma drugs based on renal recovery in this patient population (refer to Appendix 4.4). No clinical studies have been conducted and no literature data exists to evaluate the effect of RI on PK of dexamethasone.

### 3.3.4 *Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?*

Yes. A management strategy is required for the concomitant medications described below based on the Decadron labeling and literature (see Appendix 4.3). Dose adjustments of dexamethasone are prevalent in myeloma patients, especially in heavily pretreated patients, due to cumulative steroid toxicities.

Effect on Dexamethasone

*CYP3A4 Modulators:*
Avoid concomitant use of strong CYP3A inhibitors or inducers, and consider alternative medication with no or minimal potential to inhibit or induce CYP3A4. If concomitant use of strong CYP3A4 inhibitors cannot be avoided, closely monitor for adverse drug reactions. If concomitant use strong CYP3A4 inducers cannot be avoided, consider increasing the dose of HEMADY.

Decadron labeling recommends to consider the risk-benefit for the concomitant use of dexamethasone with strong CYP3A4 inhibitors, and if coadministered with a strong CYP3A4 inhibitor, monitor for adverse reactions of dexamethasone.

Decadron labeling indicates ketoconazole, a strong CYP3A4 inhibitor, is reported to decrease the metabolism of certain corticosteroids by up to 60%, and moderate CYP3A inhibitors has the potential to increase dexamethasone concentrations. Literature data suggests that dexamethasone exposure increased by 4-fold with itraconazole (strong CYP3A inhibitor), and by 2-fold with aprepitant (moderate CYP3A inhibitor) (see Appendix 4.3) in subjects. Also, macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (Decadron labeling).

Decadron labeling indicates that if dexamethasone is used concomitantly with strong CYP3A4 inducers, consider increasing the dose of dexamethasone. Also, literature data indicates that coadministration of phenytoin, a strong CYP3A inducer, decreased dexamethasone bioavailability by 60% and increased dexamethasone clearance by 3-fold compared to dexamethasone alone in patients (see Appendix 4.3).

*Other Drugs*:

*Cholestyramine:* Cholestyramine may increase the clearance of corticosteroids (b) (4) (Decadron labeling). Avoid coadministration of cholestyramine and HEMADY and consider use of alternative (b) (4).

*Ephedrine: Consider i*ncreasing the dose of HEMADY when coadministered with ephedrine, as ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity (Decadron labeling).

*Estrogens, including oral contraceptives:* Estrogen may decrease the hepatic metabolism of certain corticosteroids, (b) (4) (Decadron labeling).

*Anti-myeloma drugs:* No dose adjustment of HEMADY with thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib or carfilzomib. Co-administration of thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib, or carfilzomib with dexamethasone is not expected to affect the PK of dexamethasone (see Appendix 4.3).

Effect of Dexamethasone:

*CYP3A4 substrates*: Dexamethasone is a moderate inducer of CYP3A4 and co-administration with other drugs that are metabolized by CYP3A4 may increase clearance and decrease plasma concentration of these drugs (Decadron labeling).

*Nonsteroidal anti-inflammatory agents (NSAIDS):* Monitor for toxicity when aspirin is used in conjunction with HEMADY in hypoprothrombinemia. Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. The clearance of salicylates may be increased with concurrent use of corticosteroids (Decadron labeling).

*Phenytoin:* In post-marketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone coadministration, leading to alterations in seizure control. (Decadron labeling).

*Potassium depleting agents:* Closely monitor patients for hypokalemia when potassium depleting agents (e.g., amphotericin B, diuretics) when coadministered with HEMADY. Sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids. Also, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (Decadron labeling).

*Digitalis glycosides:* Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia (Decadron labeling).

*Oral Anticoagulants:* Frequently monitor coagulation indices to maintain the desired anticoagulant effect in patients on anticoagulant therapy (e.g., warfarin) when administered with HEMADY, as corticosteroids may reduce the response to anticoagulants (see Appendix 4.3, and Decadron labeling).

*Antidiabetic Drugs:* Consider adjusting the dose of antidiabetic drugs, as necessary, when coadministered with HEMADY, as corticosteroids have been reported to increase blood glucose concentrations (see Appendix 4.3, and Decadron labeling).

*Isoniazid:* Serum concentrations of isoniazid may be decreased (Decadron labeling).

*Thalidomide:* Closely monitor for toxicity when thalidomide is coadministered with HEMADY. Toxic epidermal necrolysis has been reported with concomitant use of thalidomide (Decadron labeling).

*Vaccines:* Patients on corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. If possible, defer routine administration of vaccines or toxoids until HEMADY therapy is discontinued (Decadron labeling).

*Concomitant Therapies that may Increase the Risk of Thromboembolism:* Thromboembolism is a known adverse reaction of dexamethasone (Decadron labeling). The risk for venous and arterial thromboembolism increases significantly when dexamethasone is administered with anti-myeloma drugs (Thalomid, Revlimid, Pomalyst labeling). Monitor for risk of thromboembolism in patients with MM receiving anti-myeloma products with HEMADY.

*Anti-myeloma drugs:* No dose adjustments for thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib or carfilzomib when coadministered with HEMADY. Dexamethasone is not expected to affect the PK of thalidomide, lenalidomide, pomalidomide, ixazomib, bortezomib and carfilzomib (see Appendix 4.3)

### *3.3.5 Does this drug prolong the QT or QTc interval?*

Literature data suggests dexamethasone may not have the potential for QT prolongation (see Appendix 4.5).

## 4. APPENDICES

### 4.1 Bioequivalence Study

The Applicant conducted an open label, single-dose, randomized, three-treatment, three-period crossover study to compare the bioavailability of HEMADY Tablet, 20 mg (test) against the approved West-Ward's Dexamethasone 4 mg tablet (reference) under fasting conditions, and HEMADY Tablet, 20 mg under fasting and fed conditions (Table 4).

Table 4: Design of Study 160458

| Purpose | Parameters |
|---|---|
| **Study Design** | 3-treatment, 3-sequence, cross-over study. 7-day washout. The subjects were randomized to one of three sequences [test (fast) reference (fast) test (fed); reference (fast) test (fast) test (fed); test (fed) reference (fast) test (fast)] for dosing. |
| **Study Population** | 36 healthy subjects enrolled. 34 subjects completed the study |
| **Proposed Dose** | 20 mg single dose<br>Under fasting conditions, no food was allowed from at least 10 hours before dosing until at least 4 hours after dosing. Under fed conditions, a high-fat, high-calorie meal (total 800-1000 calories: 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) was served 30 minutes prior to dosing and subjects fasted for at least 4 hours after dosing. |
| **PK Sampling Schedule** | Predose (0 hr), and at 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10.0, 12, 16, 20, 24, and 36 hours post-dose. |
| **ECG Monitoring Schedule** | Before first infusion, 180 min after the end of first infusion (i.e., 360 min after start of infusion), and 24 hours after the second infusion (and on Day 7 if clinically indicated). |

The protocol criteria for bioequivalence was that the 90% confidence intervals of the geometric mean ratios (GMR) for peak concentration (Cmax), area under the concentration time curve (AUC) to the last time point ($AUC_{0-t}$) and $AUC_{0-\infty}$ should be within 80%-125%. No food effect was concluded if the 90% CI of GMR were within 80 to 125%. Summary BE statistics and descriptive statistics of the PK parameters of dexamethasone are presented in Table 5 and Table 6.

Table 5: Summary BE Statistics (Plasma Dexamethasone), Study 160458 (n=34)

| Parameter (unit) | Least Squares Geometric Mean (n=34) | | Ratio of Test / Reference | 90% Confidence Interval of Ratio |
|---|---|---|---|---|
| | Dexamethasone Tablet, 1x20 mg | Dexamethasone Tablet, 5 x 4 mg | | |
| $AUC_{0-t}$ (h*ng/mL) | 1254 | 1262 | 99.4 | 95.66 – 103.22 |

| | | | | |
|---|---|---|---|---|
| **$AUC_{0-\infty}$ (h*ng/mL)** | 1267 | 1277 | 99.2 | 95.46 – 103.10 |
| **Cmax (ng/mL)** | 246.4 | 231.8 | 106.3 | 97.71 – 115.63 |
| **Parameter (unit)** | **Dexamethasone Tablet, 1x20 mg (n=33)** | | **Ratio of Fed / Fast** | **90% Confidence Interval of Ratio** |
| | **Fed** | **Fast** | | |
| **$AUC_{0-t}$ (h*ng/mL)** | 1276 | 1237 | 103.1 | 99.15 – 107.33 |
| **$AUC_{0-\infty}$ (h*ng/mL)** | 1293 | 1251 | 103.4 | 99.30 – 107.60 |
| **Cmax (ng/mL)** | 186.4 | 241.8 | 77.1 | 69.45 – 85.54 |

Source: Reviewer's analysis

**Table 6:** Geometric Mean PK Parameters of Dexamethasone, Study 160458

| Variable | Dexamethasone Tablet, 1x20 mg | Dexamethasone Tablet, 5 x 4 mg | Dexamethasone Tablet, 1x20 mg |
|---|---|---|---|
| **Food Status** | **Fasted** | **Fasted** | **Fed** |
| **N** | 34 | 34 | 33 |
| **$AUC_{0-\infty}$ (h*ng/mL)** | 1271.01 (30.99) | 1275.25 (34.03) | 1293.97 (32.64) |
| **$AUC_{0-t}$ (h*ng/mL)** | 1257.28 (30.96) | 1259.35 (33.97) | 1277.04 (32.56) |
| **Cmax (ng/mL)** | 246.48 (30.90) | 231.38 (35.07) | 185.61 (32.86) |
| **T½ (hr)*** | 3.91 (18.04) | 3.95 (16.59) | 4.00 (19.62) |
| **Tmax (hr)**** | 1.00 | 1.50 | 2.50 |

*Arithmetic mean (%CV), **Median (range)
Source: Reviewer's analysis

The 90% confidence intervals of the GMR for Cmax, AUC0-t, and AUC0-∞ were within the acceptable BE limits of 80% to 125% between HEMADY tablet, 20 mg (test) and the West-Ward's Dexamethasone 4 mg tablet (reference) under fasting conditions (Table 5,

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). Therefore, the HEMADY 20 mg tablet and West-Ward's 5 x 4 mg Dexamethasone tablets are bioequivalent.

Also, there was no effect of high calories, high-fat meal on dexamethasone AUC, as the 90% CI of the GMR for AUC0-t, and AUC0-∞ were within the acceptable BE limits of 80% to 125%

compared to fasting conditions(Table 5, Figure 2), however, the Cmax was reduced by 23% with high-fat meal.

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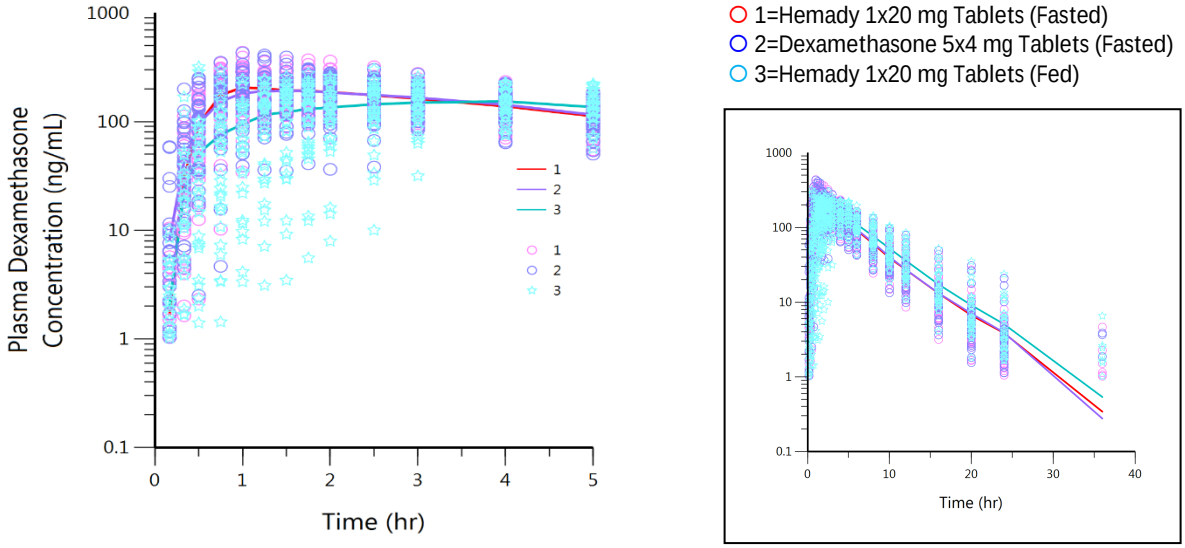
Figure 2: Log-linear Time-dexamethasone concentration profile (inset: time to 36 hour)




## Safety

From a safety perspective, there were greater incidence of AEs with Dexamethasone 5 x 4 mg Tablets compared to Dexamethasone 1 x 20 mg Tablets. Following a 20 mg dose, 10-14 subjects had 31-35 AEs after administration of Dexamethasone tablets. Headache, dizziness and viral upper respiratory infections were the commonly reported AEs for both formulations. Two subjects reported significant AEs:

- Subject (b) (6) experienced viral upper respiratory tract infection, and increased heart rate and blood pressure after treatment with Dexamethasone 5 x 4 mg Tablets (Period 2). The AEs were of mild severity, were not resolved by the end of the study and judged as clinically significant but unrelated to medication, and the subject was withdrawn;
- Subject (b) (6) experienced "Influenza like illness" for 15 days after treatment with HEMADY 1 x 20 mg Tablet (Period 1). The AE was moderate to severe, and was resolved with treatment. The subject did not show up in Period 2, and was withdrawn prior to Period 3.

- Subject (b) (6) completed Period 1 and 3 but withdrew consent in Period 2.

Table 7. Incidence of Adverse Events (Study 160458)

| | Dexamethasone, 1 x 20 mg Tablet | | Dexamethasone 5 x 4 mg Tablet |
|---|---|---|---|
| Incidence (% subjects) | Fasting | Fed | Fasting |
| Patients | 9 | 8 | 16 |
| Adverse events (AE)<br>Drug-related | 17<br>10 (33.3%) | 17<br>12 | 31<br>16 |
| Severe AEs | 16 | 15 | 28 |
| AE leading to deaths | 0 | 0 | 0 |

In summary, the bioequivalence study demonstrates that the HEMADY tablet and West-Ward's dexamethasone tablet are bioequivalent with respect to AUC and Cmax, and there was no effect of food on the exposure of HEMADY tablet. Also, no clinically meaningful differences in AEs were observed between the two formulations.

## 4.2 Dexamethasone PK Data from Literature

The following PK data was available from literature and the application (Table 8):

Table 8: Summary of dexamethasone PK data from literature

| Reference | Dose, mg | Population | Oral Form. | Strength (mg) | N | Mean (CV) | | | | LLOQ (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | CL (L/hr) | AUC (ng*hr/mL) | Cmax (ng/mL) | T½ (hr) | |
| Duggan, 1975[3] | 12 | Subjects | Tablet[a] | 1.5 | 12 | 12.1† | 996* | -- | -- | 1 |
| | 12 | Subjects | Elixir[a] | | | 12.6† | 953* | -- | -- | |
| Loew, 1986[4] | 0.5 | Subjects | Tablet | 0.5 | 10 | 10 (23) | 58 (19)* | 8 | 5.2 (58%) | 0.1 |
| | 1.5 | Subjects | | 1.5 | | 15.6 (31) | 113 (34)* | 14 | 6.6 (65%) | |
| Egerman, 1997[5] | 8 | Subjects | Tablet | 4 | 8 | 22.3† | 359 (27) | 66 (32) | -- | 1 |
| Kovarik, 1998[6] | 8 | Subjects | Tablet | 4 | 18 | 20.0† | 400 (22) | 88 (26) | 3.7 (27) | 5 |
| Toth, 1999[7] | 200 | Patients | Capsule[b] | 100 | 4 | 21.4† | 9360 (25) | 1980 | 1.9 (48) | 25 |
| | 300 | Patients | | | 3 | 19.7† | 15230 (4) | 3220 | 2.0 (11) | |
| McCrea, 2003[8] | 20 | Subjects | Oral | ? | 20 | 22.3† | 897* | 179 | 3.6 | 0.25 |
| | 8 | Subjects | Oral | ? | | 27.4† | 292* | 58 | 3.9 | |
| Harahap, 2009[9] | 4 | Subjects | Tablet | 4 mg | 24 | 7.7† | 519 / 502* | 98 | 3.4 | 1 |
| | | Subjects | Tablet | 4 mg | | 7.6† | 525 / 507* | 98 | 3.4 | |
| Marbury, 2011[10] | 8 | Subjects | Oral, D1 | 8 mg | 13 | 22.0† | 364* | 70 | 3.6 | 0.5 |
| | | | Oral, D2 | | | 28.3† | 283*[c] | 63 | 3.0 | |

[3] Duggan et al. (1975). *Clin Pharmacol Ther* 18 (2): 205-209
[4] Loew et al. (1986) *Eur J Clin Pharmacol* 30(2): 225-230
[5] Egerman et al. (1997). *Obstet Gynecol* 89(2): 276-280
[6] Kovarik et al. (1998). *Pharmacotherapy* 18(6): 1230-1236
[7] Toth et al. (1999). *Ther Drug Monit* 21(5): 532-535.
[8] McCrea et al. (2003). *Clin Pharmacol Ther* 74(1): 17-24
[9] Harahap et al. (2009). *Arzneimittelforschung* 59(4): 191-194
[10] Marbury et al. (2011). *J Clin Pharmacol* 51(12): 1712-1720

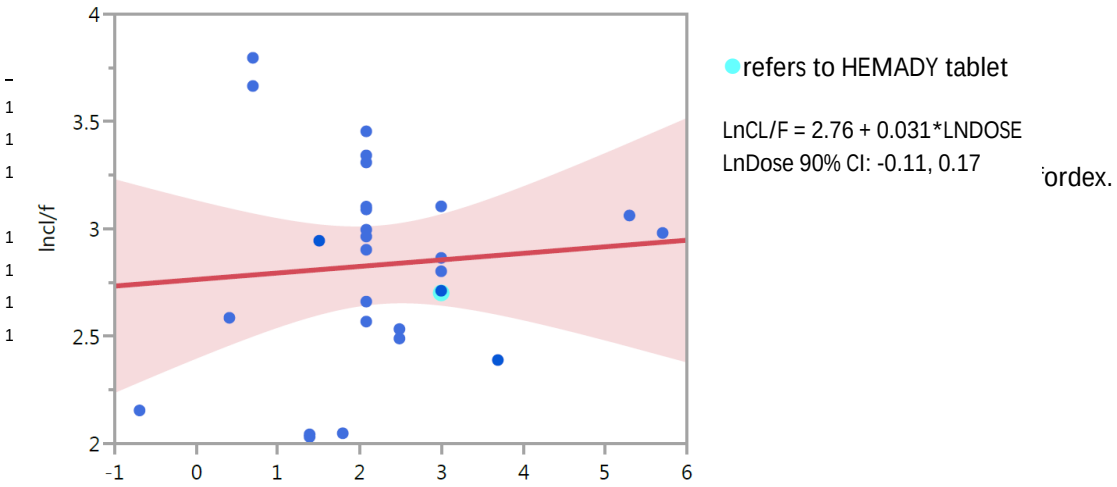
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Oral, D3 | | | 31.6† | 253*[c] | 57 | 3.1 | |
| Queckenberg, 2011[11] | 2 | Subjects | Soln | 2 mg/mL | 24 | 44.5† | 46 (39)/38 (38)* | 9 (32) | 4.5 (72) | 0.7 |
| | 2 | Subjects | Tablet | 2 | | 39.1† | 48 (40)/41 (41)* | 9 (33) | 3.9 (49) | |
| Spoorenberg, 2013[12] | 6 | Patients | Tablet [d] | 1.5 | 30 | 7.7 | 774 | -- | 6.9 | 2.5 |
| Neofordex, 2015[13] | 20 | Subjects | | 0.5 | 24 | 17.5† | 1140 (32) | 126 (18) | 4.6 (27) | 1 |
| | 20 | Subjects | Tablet | 40 | | 16.5† | 1214 (35) | 214 (25) | 4.0 (30) | |
| Toledo, 2015[14] | 8 | Subjects | Soln | 1 mg/mL | 11 | 13.0† | 614 (42) | 94 (16) | 2.6 (39) | 2 |
| | 8 | Subjects | Soln | 4 mg/mL | | 14.31† | 559 (55) | 79 (29) | 2.9 (35) | |
| Diamant, 2017[15] | 8 | Subjects | Tablet | 8 | 30 | 19.4† | 413 (33) | 73 (26) | 4.2 (21) | ? |
| | 8 | Subjects | | 4 | | 18.2† | 439 (35) | 73 (25) | 4.2 (18) | |
| Study 160458 | 20 | Subjects | Tablet | 20 | 34 | 15.7† | 1271/1257* | 247 (31) | 3.9 (18) | |
| | 20 | Subjects | Tablet | 4 | | 15.7† | 1275/1259* | 232 (35) | 4.0 (17) | |
| Iida 2010[16] | 40 | Patients | Tablet | 40 | 6 | 11 (44) | 3661/3528* (38) [e] | 499 (33) | 4.2 (32) | ? |
| Varis 2000[17] | 4.5 | Subjects | Tablet [f] | 1.5 | 8 | 19† | 239 (22) | 38 (42) | 4 (24) | 2 |

*0-24 hours; †estimated based on Dose/AUCinf
[a] Mean Absolute BA 78% and 86%.
[b] Mean Absolute BA 61-65%
[c] Racc 0.70 to 0.76.
[d] Mean Absolute BA 81%
[e] Racc 0.76
[f] Mean Absolute BA 75%

## Dose Proportionality

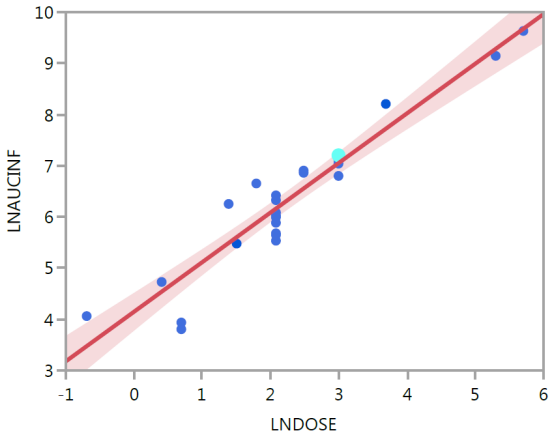
The dose proportionality of PK of oral dexamethasone was investigated based on literature data from 15 references, consisting of 28 doses between 0.5 and 300 mg (Table 8): 75% (24 of 28) were conducted in healthy subjects and 96% were single dose studies. Only 21% (6 of 28) of oral doses were ≥20 mg. The database also included 11 intravenous doses between 4-200 mg. The highest proposed dose of HEMADY is 40 mg. The relationships between dose and CL/F, Cmax, and AUC were linear (Figure 3, Figure 4, Figure 5), however, there was limited PK information at doses ≥20 mg. The overall variability including all oral doses was ~45% for CL/F (19±9 L/hr), DN AUC (64±30 ng*hr/mL/mg) and DN Cmax (10.4±4.7) which is on the higher side of the PK variability (20 to 50%: Table 8) observed in literature. It should be noted that the cross-study comparison could also be contributing to the variability due to factors such as study design (e.g., sample size, PK time points) and conduct (e.g., bioanalytical measurement).

Figure 3: Relationship between Oral Dose and Clearance (CL/F).

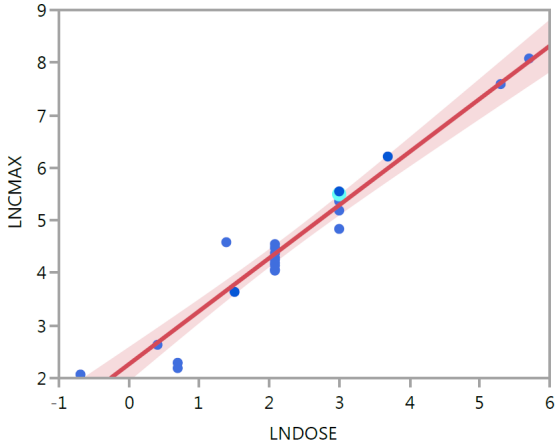



ordex.

Figure 4: Relationship between Oral Dose and AUC (left) or Cmax (right)



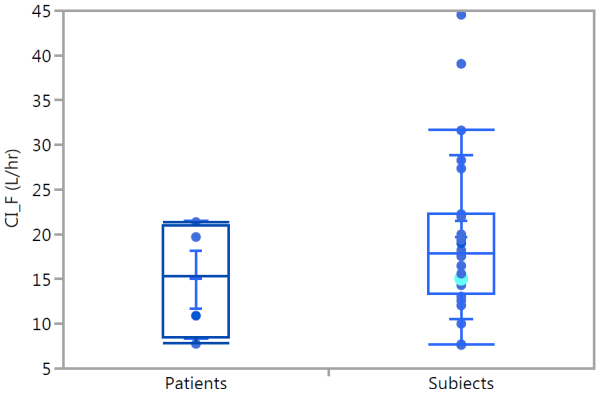

lnAUC = 4.14 + 0.97*LNDOSE
LNDOSE: 95% CI: 0.82, 1.11

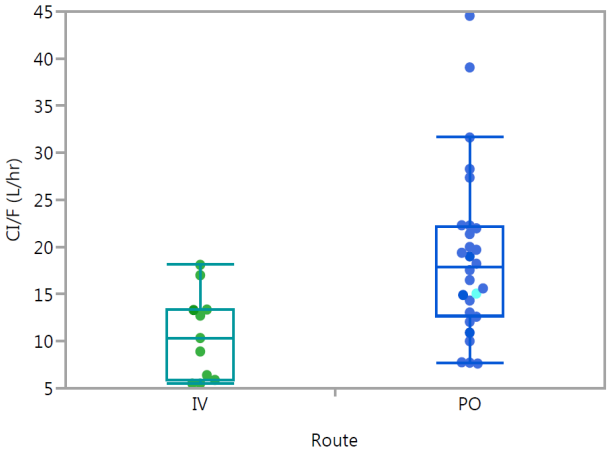



lnCmax = 2.26 + 1.01*LNDOSE
LNDOSE: 95% CI: 0.88, 1.13

● refers to HEMADY tablet

Figure 5: Clearance by Population (for oral route) (left) and route of administration (right).




● refers to HEMADY tablet

<u>Absolute Bioavailability</u>:

Absolute bioavailability of HEMADY 20 mg tablet was not evaluated by the Applicant. The absolute bioavailability reported in literature for oral dexamethasone tablets was between 60

to 80% (Table 8): ~60% for 0.5 mg tablet (O'Sullivan 1997), and 75-80% for 1.5 mg tablets (Duggan et al., 1975[3], Varis, 2000[17], and Spoorenberg et al., 2013[12]).

Elimination and Excretion

Dexamethasone is metabolized by CYP3A4 in vitro. The major metabolite is 6ß-hydroxy-dexamethasone (Gentile et al., 1996)[2]. Dexamethasone is cleared mainly via hepatic route, as renal clearance accounts for < 10% of total body clearance. Less than 10% of the dose is excreted in urine as unchanged (Brady et al., 1987[18]; Hitchen & Hogan, 1974[19]).

## 4.3 Literature DDI Studies

No clinical DDI studies were conducted by the Applicant.

Dose adjustments of dexamethasone are prevalent in myeloma patients, especially in heavily pretreated patients, due to cumulative steroid toxicities.

The following literature information supports the labeling recommendations:

Effect on Dexamethsone

Effect of Strong CYP3A Inhibitor (Varis et al., 2000)[17]:

Strong CYP3A inhibitor, itraconazole increased the exposure dexamethasone by ~4-fold. In a randomized, double-blind, placebo-controlled crossover study with four phases, 8 healthy subjects took either 200 mg itraconazole (in two phases) or placebo (in two phases) orally once daily for 4 days. On day 4, each subject received an oral dose of 4.5 mg dexamethasone (3 x 1.5 mg Dexamethasone tablets; Orion Pharma, Espoo, Finland) or an intravenous 5.0 mg dexamethasone during both itraconazole and placebo phases. Compared with placebo, the $AUC_{0-\infty}$ and $C_{max}$ of orally administered dexamethasone was increased by 3.7-fold ($P < .001$) and 1.7-fold ($p<0.001$), respectively, by itraconazole.

Mean cortisol levels following dexamethasone administration decreased by ≥90% from baseline by 12 hours, and after 23 hours, cortisol levels increased and returned to baseline levels by 71 hours after dexamethasone administration.

PK samples were collected up to 71 hours post-dose. Dexamethasone and cortisol were measured by HPLC with a LLOQ of 2 ng/mL and the interday assay CV less than 9% for the dexamethasone assay and a LLOQ of 5 ng/mL and the interday assay CV less than 7%. Neither itraconazole nor hydroxyitraconazole interfered with the dexamethasone assay. The absolute bioavailability of dexamethasone tablet was 75%.

Effect of Moderate CYP3A Inhibitor (McCrea et al., 2003)[8]:

Aprepitant, a moderate CYP3A inhibitor, increased the exposure of dexamethasone by ~2-fold. However, dexamethasone exposure with aprepitant was similar after halving the dexamethasone dosing regimen with aprepitant compared to that of a full dexamethasone dosing regimen alone (see Table 9).

[18] Brady et al. (1987). *Eur J Clin Pharmacol* 32: 593-596
[19] Hitchen & Hogan (1974). *Clin Chem* 20(2):266-271

Table 9: Effect of aprepitant on dexamethasone PK.

| | GMR B/A (90% CI) | | GMR C/A (90% CI) | |
|---|---|---|---|---|
| | Day 1 | Day 5 | Day 1 | Day 5 |
| $AUC_{24hr}$ | 2.17 (1.95, 2.40) | 2.20 (1.89, 2.55) | 1.29 (1.17, 1.44) | 1.03 (0.89, 1.20) |
| $C_{max}$ | 1.35 (1.12, 1.64) | 1.52 (1.21, 1.90) | 0.85 (0.70, 1.03) | 0.79 (0.63, 0.99) |

Source: McCrea et al. (2003). Clin Pharmacol Ther 74(1): 17-24

This was an open-label, randomized, 3-period crossover study. Twenty subjects were administered the following treatments:

- Treatment A: standard oral dexamethasone (formulation and strength not specified) regimen - 20 mg on day 1, and 8 mg on days 2 to 5;
- Treatment B: effects of oral aprepitant -125 mg on day 1, and 80 mg on days 2 to 5 on the standard dexamethasone regimen.
- Treatment C: effects of oral aprepitant on modified dexamethasone regimen-12 mg on day 1, and 4 mg on days 2-5.

All subjects also received 32 mg ondansetron intravenously on day 1 only.

Dexamethasone PK sampling was collected up to 24 hours post-dose on Day 1 and 5. Dexamethasone was measured by LC/MS/MS assay between 0.25-500 ng/mL. The assay accuracy and precision were 1-8% & 1-7%, respectively

Effect of Strong CYP3A Inducer (Chalk et al., 1984)[20]

Of 16 subjects who received dexamethasone therapy for various neurological or neurosurgical conditions, 6 received phenytoin, 9 did not receive phenytoin at any time, and 1 patient was studied twice, once before and once during phenytoin. Patients received a single IV dose of 4 mg dexamethasone. Mean oral bioavailability of dexamethasone was significantly ($p<0.005$) reduced by 60% in patients taking dexamethasone with phenytoin (0·33 ± SD 0·33) versus patients on dexamethasone alone (0·84 ± 0·23). Systemic clearance significantly increased ($p <$ 001) in patients taking dexamethasone with phenytoin (0·798 ± 0·479 L/hr/kg) compared to patients on dexamethasone alone (0·272 ± 0·129 L/hr/kg). Mean terminal plasma half-life (3·34 ± 1· 15 hours) was longer than in those who had received phenytoin (1·81 ± 1·78 hours), however, the difference was not statistically significant ($p > 0·05$).

Dexamethasone PK samples were collected up to 8 hours post-dose, and measured by HPLC. However, assay performance was not provided.

Effect of Ephedrine (Brooks et al., 1977)[21]

The effect of ephedrine on dexamethasone metabolism was studied in nine asthmatic patients before and after administration of 100 mg ephedrine daily for three weeks . Five patients were studied similarly but treated with placebo. The patients were administered labeled dexamethasone intravenously. With ephedrine, a 36% ($p<0.025$) decrease in plasma dexamethasone half-life ($t_{1/2}$), and a 42% ($p<0.001$) increase in metabolic clearance rate (MCR) were observed. Increase in the excretion of urinary radioactivity, predominantly in the conjugated fractions, was noted.

Effect of Thalidomide, Lenalidomide, Pomalidomide, Ixazomib, or Bortezomib:

[20] Chalk *et al*. (1984). *J Neurol Neurosurg Psychiatry* 47(10): 1087-1090.
[21] Brooks *et al.* (1977). *J. Clin Pharmacol.* 17(5-6): 308-318.

The Thalomid, Pomalyst, and Ninlaro labeling indicate that thalidomide, pomalidomide, and ixazomib are not CYP or CYP3A inhibitors or inducers in vitro. Literature data suggests that lenalidomide is not a CYP inhibitor or inducer in vitro (Clinical Pharmacology review of Revlimid at Drugs@FDA, and Kumar et al., 2017[22]). Also, literature data suggests that bortezomib and its metabolites do not inhibit CYP3A, and there was no time-dependent inhibition of CYP3A in vitro (Lu et al., 2006[23]). Therefore, thalidomide, lenalidomide, pomalidomide, and ixazomib are not expected to have an effect on dexamethasone PK.

Effect of Panobinostat and Carfilzomib:
Per Farydak and Kyprolis labeling, panobinostat and carfilzomib are time dependent inhibitors of CYP3A but not inducers of CYP3A in vitro. Also, drug labeling indicates that panobinostat and carfilzomib show negligible or no effect on midazolam exposure. Therefore, panobinostat and carfilzomib are not expected to have an effect on dexamethasone PK.

Effect of Dexamethasone
Lenalidomide:
Co-administration of a single dose or multiple doses of dexamethasone (40 mg) had no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (Revlimid labeling).

*Iida et al., 2010*[16]
In 6 patients enrolled in the combination cohort (25 mg lenalidomide on Days 1-21, and 40 mg of dexamethasone on days 1–4, 9–12, and 17–20 for the first 4 cycles and only on days 1–4 after the 4th cycle.), the PK of lenalidomide were not clinically significant with and without dexamethasone [$AUC_{0-\infty}$1890 (17) vs. 2177 (13) ng•h/mL], $C_{max}$ [433 (46) vs. 474 (27) ng/mL, and CL/F 221 (17) vs. 191 (13) mL/min].

Blood samples for lenalidomide and dexamethasone were collected up to 24 hours (Iida et al., 2010). The concentrations of R and S-lenalidomide in plasma were determined by chiral liquid chromatography–tandem mass spectrometry (LC–MS/MS). The concentration of dexamethasone in plasma was determined by LC–MS/MS. However, assay performance was not provided.

*Hou et al., 2013*[24]
Lenalidomide PK at steady state were similar with and without 40 mg oral dexamethasone in patients (n=11): $AUC_{0-\infty}$ (%CV) of 2162 (43) vs. 2141 (45) ng•h/mL.

Pomalidomide
Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. Co-administration of multiple doses of 4 mg POMALYST with 20 mg to 40 mg dexamethasone to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared to when pomalidomide was administered alone (Pomalyst Labeling).

Bortezomib

[22] Kumar et al. (2017). *Cancer Chemo Pharmacol.* 63:1171
[23] Lu et al. (2006). *Drug Metab Disp* 34(4):702-708
[24] Hou et al. (2013). *J Hematol Oncol* 6: 41

No clinically significant differences in bortezomib pharmacokinetics were observed when coadministered with dexamethasone (Velcade labeling).

*Hellmann et al., 2012*[25]
Based on literature data, dexamethasone had no effect on mean $AUC_{72h}$ (%CV) of bortezomib: 179 ng•h/mL (61%) in Cycle 2 vs 170 ng•h/mL (65%) in Cycle 3 in patients with MM. Patients received intravenous bortezomib 1.3 mg/m$^2$ (on days 1, 4, 8 and 11 of a 21-day cycle) for 3 cycles, and with oral dexamethasone 40 mg once daily on days 1–4 and days 9–12 during cycle 3 only. Blood samples were collected on days 11 through 14 (up to 72 hours) of cycles 2 and 3. Bortezomib was determined using a LC/MS/MS, with a quantification range of 0.1–25 ng/mL.

Anticoagulants:
*Sellam et al, 2007*[26]
High dose dexamethasone can potentiate oral anticoagulants and elevate anticoagulant indices. Nine patients with multiple myeloma or AL amyloidosis taking daily doses of oral fluindione (n=8: 10 to 35 mg) or warfarin (n=1: 4 mg), were studied for a total of 10 cycles. Oral dexamethasone (40 mg/day for 4 days every 28 days) was administered alone (n=4) or with melphalan (n=5). The mean International normalized ratio (INR) significantly increased (p=0.01) in 8 of 9 patients: overall INR increased by 90% after dexamethasone. The mean fluindione and warfarin concentrations increased 37% (p=0.01) and 28%, respectively, from baseline after dexamethasone administration. In controls receiving dexamethasone without oral anticoagulants, there was no increase prothrombin time.

INR was measured serially during dexamethasone administration. Prothrombin time, interpreted as the INR, was measured with Simplastin Excel S reagent with an international sensitivity index of 1.31 (Organon Teknika Corp., Durham, NC). There was no in vitro interference between dexamethasone and INR reagents. Total plasma (free and bound) fluindione and warfarin concentrations were measured for 5 cycles by HPLC. The minimum detectable concentration of fluindione was 50 ng/mL and of warfarin 20 ng/mL.

*Hazelwood et al., 2006*[27]
A retrospective review was conducted of 387 medical records for active patients within an anticoagulation clinic. Patients with stable anticoagulation therapy, short-term oral corticosteroid therapy, pre- and during/post-INR assessment were included. Thirty-two patient encounters met the predetermined inclusion and exclusion criteria. The primary outcome assessed was the difference between pre- and post-INR values.

Thirty one of 32 patient encounters resulted in a change in their post-INR value, and 62.5% of patients had supratherapeutic INR values at the post-corticosteroid assessment. The majority of patients assessed had an elevation of their INR following concomitant use of warfarin and corticosteroids. The mean difference between pre- and post-INR values was 1.24 (95% CI 0.86 to 1.62). Overall, 16 patients (50%) required a modification of their anticoagulation therapy during or following corticosteroid therapy.

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[25] Hellmann et al. (2012). *Clin Pharmacokinetics* 50(12):781-791
[26] Sellam et al. (2007). *Joint Bone Spine* 74:446-452.
[27] Hazlewood et al. (2006). *Ann. Pharmacother.* 40(12):2101-2106.

## 4.4 Organ Impairment

There are no recommendation for organ impairment in the current Decadron labeingl[Error! Bookmark not defined.]. The available literature data do not provide sufficient information for dexamethasone dosing recommendations for organ impairment. Literature data suggests that dexamethasone is primarily metabolized in the liver. Less than 10% is excreted unchanged in urine, about 60% was recovered as inactive metabolites.

Literature Data: Renal Impairment

*Dimopoulos et al., 2016*[28]

Following review of available evidence on management of patients with MM with renal impairment (RI), the International Myeloma Working Group (IMWG) proposed no adjustments for patients with MM with moderate to severe RI (creatinine clearance, CLcr >30 mL/min) or ESRD (CLcr <15 mL/min), and on hemodialysis. Per IMWG, conventional chemotherapy with standard-dose corticosteroids produces 25% to 50% of renal recovery. Also, high-dose corticosteroids (equivalent to dexamethasone ≥ 160 mg over 4 days; dexamethasone 40 mg, 4 days on and 4 days off, for 3 pulses in a 28-day cycle) are effective in improving RI compared with conventional doses of corticosteroids. The administration of high-dose dexamethasone, ≥ 160 mg in the first month of therapy, was associated with a more rapid renal response, even in patients treated with immunomodulatory drugs (IMiDs) or bortezomib, in a retrospective analysis of 133 patients with newly diagnosed myeloma with RI (1.6 vs 46 months for doses of < 160 mg; *P* = .008).

*Kwai et al., 1985*[29]

16 patients with renal failure and 16 subjects with normal renal function were administered 1 mg of dexamethasone (along with 1 mg cortisol and 1 mg prednisolone) as IV bolus. The mean half-time for plasma disappearance (t½) of dexamethasone was significantly shortened (2.4 hours vs. 3.5 hours, p<0.01) and mean metabolic clearance rate (MCR) of dexamethasone was significantly increased (259 L/day/$m^2$ vs. 153 L/day/$m^2$, p<0.02) in patients with renal failure compared to normal subjects. However, the RI classification (based on baseline CLcr) of patients with renal failure were widely distributed, with 1 moderate RI (48 mL/min), 5 severe RI (29-15 ml/min), 3 ESRD (<15 ml/min), and 7 on hemodialysis. In addition, the MCR values for patients with renal failure were skewed in that the majority of patients on hemodialysis had MCR < mean (259 L/d/$m^2$), while the MCR of the majority of remaining patients were > the mean. Therefore, the impact baseline renal impairment on the PK of dexamethasone cannot be discerned.

Blood was collected predose, and every hour for 5 hours post-dose, and plasma levels of dexamethasone was measured by RIA.

Literature Data: Hepatic Impairment

Twenty patients with chronic liver disease, and 16 normal subjects were administered 1 mg of dexamethasone (along with 1 mg cortisol and 1 mg prednisolone) as IV bolus (Kwai et al., 1985[29]). The mean t½ of dexamethasone was significantly prolonged in liver disease (5.9 ± 2.2 h vs. 3.5 ± 1.0 h; *P* < 0.001) and MCR of dexamethasone was significantly decreased (98 ± 43

[28] Dimopoulus et al. (2016). *J Clin Oncol* 34(13):1544-1557.

[29] Kawai et al. (1985). J Clin Endocrinol Metab 60(5): 848-854

L/day•m$^2$ vs. 153 ± 45 L/day•m$^2$; $P < 0.01$) in patients with liver disease compared with that in normal subjects. However, the hepatic classification of patients with chronic liver disease was not provided, as only AST levels were provided.

## 4.5 QT Prolongation

Dexamethasone can be safely administered as part of an anti-emetic regimen in patients with LQTS (O'Hare at al., 2018[30]). Dexamethasone was reported to suppress drug-induced QT prolongation in a patient (Winterfield and Milan, 2016[31]).

## 4.6 Bioanalytical Method Report

Dexamethasone was assessed in the EDTA plasma of subjects in Study 160458 by LC/MS/MS following liquid-liquid extractions. The assay was validated for the quantitation of dexamethasone in human plasma over the range of 1 ng/mL to 1000 ng/mL. The sponsor states the method validation met the established acceptance criteria. Samples with concentration levels above the ULOQ (>1000 ng/ml) may be analyzed by applying a maximum of a 20-fold dilution.

Table 10: Summary of Assay validation results

| Validation Parameters | | Dexamethasone | |
|---|---|---|---|
| Assay | | Liquid-Liquid extraction with LC/MS/MS | |
| Blank Matrix | | Human EDTA $K_2$ Plasma | |
| Internal Standard | | Dexamethasone-$d_4$ | |
| Calibrator levels: | | 1, 2, 20, 100, 200, 400, 800, & 1000 ng/mL | |
| Quality Control levels | | 1 (LLOQ), 3 (low), 500 (Med), & 750 (High) ng/mL | |
| Quality Control Samples | | Accuracy (% target) | Precision (%CV) |
| Inter-batch | LLOQ | 2% | 7.6% |
| | Low | 3.9% | 6.4% |
| | Medium | 2.5% | 1.6% |
| | High | 0.9% | 3.8% |
| Intra-batch | LLOQ | 5.5%-11.2% | 2.8% - 9.2% |
| | Low | -3.6% to 8.6% | 1.4% to 11.4% |
| | Medium | 1.8% to 3.4% | 0.8% to 2.6% |
| | High | -2.5% to 7.3% | 0.7% to 2.7% |
| Recovery of Analyte (Internal Standard): | | 72 to 77 % (112%) | |
| Dilution Integrity (20 x): | | Bias: 14.5 %, CV: 1.2 % | |
| Matrix Selectivity (Including Hemolyzed Matrix at 5% and Hyperlipemic Matrix): | | 8 of 8 lots met acceptance criteria. Matrix factor: 1.0 (2.2% CV) at 3 ng/mL & 1.0 (0.9%) at 1000 ng/mL. | |
| Concomitant Drugs: | | Bias <13% | |
| Carryover of Analyte and IS: | | No significant carryover observed | |

[30] O'Hare et al. (2018).British J Anaesthesia 120(4): 629-644.
[31] Winterfield and Milan (2016). HeartRhythm Case Rep 2(4):280-282.

| | |
|---|---|
| **Freeze and Thaw Stability in Matrix:** | 4 cycles at -20°C and -80°C |
| **Short-Term Stability of Analyte in Matrix:** | 23.9 hours at room temperature<br>24.2 hours at 4°C |
| **Long-Term Stability of Analyte in Matrix:** | 301 days at -20°C and -80°C |
| **Stability of Analyte in Whole Blood:** | 120 minutes at room temperature<br>240 minutes in an ice/water bath |
| **Extract Stability:** | 23.1 hr at 4°C |
| **Post-Preparative Stability** | 94.9 hours at room temperature |
| **Reinjection Reproducibility:** | 79.8 hours at room temperature |
| **Stability of Analyte and IS in Solution** | 25.7 hour at room temperature<br>129 (low) & 283 (high) days at -20°C |

Study 160458

In Study 160458, plasma dexamethasone levels were determined using LC/MS/MS assay as described above at inVentiv Health. A summary of the assay performance is listed in Table 11. Study samples were analyzed in 21 analytical runs (1 run failed and another run was reinjected due to poor chromatography). Only 0.2% of the study samples were reanalyzed assigned causes. The maximum duration of frozen storage of study samples (32 days) was within the validated long-term storage duration.

**Table 11:** Summary of in-study assay parameters and performance (Study 160458)

| **Analyte** | | |
|---|---|---|
| **Matrix** | Human Plasma | |
| **Standard curve concentrations (ng/mL)** | 1, 2, 20, 40, 100, 200, 400, 800, & 1000 ng/mL | |
| **QCs** | 3, 50, 500, 750 ng/mL | |
| **QC Performance:** | Inter-assay Accuracy (% target) | Inter-assay precision (%CV) |
| **3 ng/mL** | 0.7% | 3.0 % |
| **50 ng/mL** | 0.4% | 2.5% |
| **500 ng/mL** | 2.7% | 1.8% |
| **750 ng/mL** | 2.8% | 2.1% |
| **Incurred Sample Reproducibility** | 100% ≤20% difference between reanalyzed and original values | |

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