CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202714Orig1s021

OTHER REVIEW(S)

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

Memorandum

Date: September 7, 2018

To: Andrea Baines, M.D., Clinical Reviewer
Division of Hematology Products (DHP)

Jennifer Lee, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Maritsa Serlemitsos-Day, PharmD, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for Kyprolis™ (carfilzomib)

NDA: 202714/Supplement 021

In response to DHP consult request dated June 14, 2018, OPDP has reviewed the proposed product labeling (PI). This supplement (S021) provides for Efficacy supplement for addition of a once-weekly dose regimen for carfilzomib in combination with dexamethasone to the Kyprolis™ US Prescribing Information. The following pre-submission components are part of the Real-Time Oncology Review Pilot Program.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP on September 5, 2018, and are provided below.

Thank you for your consult. If you have any questions, please contact Maritsa Serlemitsos-Day, PharmD, BCPS at (301) 796-1760 or maritsa.serlemitsos-day@fda.hhs.gov.

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

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/s/

MARITSA SERLEMITSOS-DAY
09/07/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 24, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Jennifer Lee, RPM
DHP

Subject: QT-IRT Consult to NDA 202714 (SDN 222)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 8/14/2018 regarding review of the sponsor's provided QTc datasets. The QT-IRT reviewed the following materials:

- Sponsor's response to IR (NDA 202714 / SDN 236);
- Previous QT-IRT review(s) for NDA 202714 dated 03/07/2012 in DARRTS; and
- Highlights of clinical pharmacology and cardiac safety (NDA 202714 / SDN 947).

1 QT-IRT Responses

We have previously reviewed QT data from study PX-171-005 and PX-171-007 and concluded that the data supported excluding large mean increases in the QTc interval (*i.e.*, 20 ms) (DARRTS 03/07/2012) for carfilzomib. The data included in that review showed an absence of a dose- and exposure-QTc relationship. The data previously reviewed covers the exposures expected with the new dosing regimen 20/70 mg/m^2 over 30 min.

The current review focuses on QT data collected to support a clinical efficacy supplement (S-021), which includes new dosing regimen for carfilzomib. In the initial submission we were unable to locate an evaluation for QT prolongation or a justification for why such an assessment was not necessary and an information request was therefore sent to the sponsor. In the response to our information request, the sponsor referred to the two previous studies (PX-171-005 and PX-171-007) to support an absence any dose or exposure relationship for carfilzomib and QTc

and noted that there are limitations with the provided data sets in this submission due to limited time-matched carfilzomib exposure and QTcF data.

Because of the absence of an exposure and dose relationship in the previous studies, which included dosing regimens that covers the exposure that is anticipated for this new dosing regimen per the provided highlights of clinical pharmacology table, no further QTc assessment is necessary to support the new dosing regimen.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
08/24/2018

CHRISTINE E GARNETT
08/24/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	July 25, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 202714/S-021
Product Name and Strength:	Kyprolis (carfilzomib) for injection, 10 mg per vial, 30 mg per vial and 60 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Amgen
FDA Received Date:	June 1, 2018, June 12, 2018, and June 28, 2018
OSE RCM #:	2018-1253
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the proposed Prescribing Information (PI) for Kyprolis (carfilzomib) for areas of vulnerability that could lead to medication errors. Amgen submitted supplemental NDA 202714/S-021 seeking the addition of a once-weekly dose regimen for Kyprolis (20/70 mg/m^2) in combination with dexamethasone in the currently indicated patient population. This supplemental NDA is based on results from the studies, A.R.R.O.W. and CHAMPION1.

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- N/A
Other	F- N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing the addition of a once-weekly dose regimen for Kyprolis in combination with dexamethasone in the currently indicated patient population. Kyprolis will be administered as a 30-minute infusion at a starting dose of 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, the dose will escalate to 70 mg/ m^2 on Day 8 of Cycle 1. The proposed once weekly dosing has demonstrated improvement in progression-free survival (PFS) and overall response rate (ORR).

We searched ISMP to identify whether any additional medication errors occurred with Kyprolis. Our search did not identify any relevant newsletter articles. DMEPA performed a risk assessment of the proposed PI to identify deficiencies that may lead to medication errors. However, we note there is inadequate space between the numerical dose (10) and unit of measure (mg) in preparation Step 3 of Section 2.6 of the PI. We recommend a revision to the PI to improve readability of the preparation instructions.

4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed PI identified an area that can be improved to increase readability of preparation instructions. We provide a recommendation for the Division in section 4.1 below and advise that it is implemented prior to approval of this supplement.

4.1 RECOMMENDATION FOR THE DIVISION

A. Prescribing Information
    1. Section 2.6 *Reconstitution and Preparation for Intravenous Administration*
        a. In Step 3 of the Reconstitution/Preparation Steps, place adequate space between the numerical dose and unit of measure (e.g. 10 mg instead of 10mg) to improve readability.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kyprolis received on June 28, 2018 from Amgen.

Table 2. Relevant Product Information for Kyprolis	
Initial Approval Date	July 20, 2012
Active Ingredient	Carflizomib
Indication	• Kyprolis is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma. • Kyprolis is indicated as a single-agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.
Route of Administration	Intravenous Infusion
Dosage Form	For injection
Strength	10 mg per vial, 30 mg per vial, and 60 mg per vial
Dose and Frequency	<u>Kyprolis in combination with Lenalidomide and Dexamethasone (twice weekly)</u> Kyprolis is administered by a 10-minute infusion at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis. Discontinue Kyprolis after Cycle 18. *<u>Kyprolis in Combination with Dexamethasone (once weekly regimen)</u>* *Kyprolis is administered by 30-minute infusion at a starting dose if 20 mg/m^2 in Cycle 1 on Day 1. If tolerated escalate the dose to 70 mg/m^2 on Day 8 of Cycle 1.* <u>Kyprolis in Combination with Dexamethasone (twice weekly regimen)</u> Kyprolis is administered by 30-minute infusion at a starting dose if 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1. <u>Kyprolis Monotherapy</u>

	Kyprolis is administered as a 10-minute infusion twice weekly at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Day 8 of Cycle 1. OR Kyprolis is administered as a 30-minute infusion twice weekly at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1.
How Supplied	Individually packaged single-dose vial containing 10 mg, 30 mg and 60 mg of carfilzomib as a white to off-white lyophilized cake or powder.
Storage	Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 20, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Kyprolis. Our search identified seven previous label and labeling reviews[a,b,c,d,e,f,g] and one post-marketing review[h], and we confirmed that our previous recommendations were implemented.

[a] DeFronzo K. Label and Labeling Review for Kyprolis (NDA 202714). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 Feb 03. 5 p. OSE RCM No.: 2011-3708.

[b] DeFronzo K. Label and Labeling Review for Kyprolis (NDA 202714). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 Jun 12. 4 p. OSE RCM No.: 2011-3708a.

[c] Rutledge M. Label and Labeling Review Memo for Kyprolis (NDA 202714). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Jun 10. 2 p. OSE RCM No.: 2015-325.

[d] Garrison N. Labeling and Labeling Review for Kyprolis (202714/S-12). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 16. 11 p. OSE RCM No.: 2015-2620.

[e] Garrison N. Labeling and Labeling Review for Kyprolis (202714/S-15). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jul 15. 8 p. OSE RCM No.: 2016-1319.

[f] Garrison N. Labeling and Labeling Review for Kyprolis (202714/S-17). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Nov 29. 9 p. OSE RCM No.: 2017-1353.

[g] Garrison N. Labeling and Labeling Review for Kyprolis (202714/S-20). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 Nov 03. 15 p. OSE RCM No.: 2018-309.

[h] Garrison N. Post marketing Review for Kyprolis (202714). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Jun 27. 7 p. OSE RCM No.: 2017-402.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 20, 2018, 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 Nursing Long-Term Care PA Patient Safety Canada Safety
Search Strategy and Terms	Match Exact Word or Phrase: Kyprolis

D.2 Results

Our search did not identify any relevant newsletters articles.

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,[i] along with postmarket medication error data, we reviewed the following Kyprolis labels and labeling submitted by Amgen.

- Prescribing Information (Image not shown) received on June 28, 2018

G.2 Label and Labeling Images

Prescribing Information

Application 202714 - Sequence 0232 - 1.14.1 Draft Labeling -

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

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/s/

NICOLE B GARRISON
07/25/2018

HINA S MEHTA
07/26/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 2, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Jennifer Lee, RPM
DHP

Subject: QT-IRT Consult to NDA 202714

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 6/12/2018 regarding review of QTc datasets provided as a part of the pre-submission for NDA 202714/S-021. The QT-IRT reviewed the following materials:

- QTc data sets submitted to Sequence #0227 dated 06/05/2018.

1. QT-IRT Responses

Question: DHP is requesting IRT-QT review of the QTc datasets provided with the pre-submission components of Kyprolis S-21. This supplement is being reviewed under an OHOP pilot program, which allows for the early submission of data by the Applicant. The QTc datasets are provided in SDN 941 (submitted 6/12/2018).

QT-IRT's response: The submission is incomplete and we are therefore unable to perform our review of the sponsor's QT assessment. To support our review of the sponsor's QT assessment for the new dosing regimen we need the information listed below:

a. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

b. Study report

c. Statistical analysis plan

d. Clinical study protocol

e. Investigator's Brochure

f. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table

g. Annotated CRF

h. A data definition file which describes the contents of the electronic data sets

i. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).

j. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

k. Narrative summaries and case report forms for any

    i. Deaths

    ii. Serious adverse events

    iii. Episodes of ventricular tachycardia or fibrillation

    iv. Episodes of syncope

    v. Episodes of seizure

    vi. Adverse events resulting in the subject discontinuing from the study

l. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
07/02/2018

CHRISTINE E GARNETT
07/02/2018