CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217564Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: October 2, 2023

To: Craig Long, PharmD, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Andrew Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

Doris Auth, PharmD, Associate Director for Labeling, DO3

Subject: OPDP Labeling Comments for FRUZAQLA™ (fruquintinib) capsules, for oral use

NDA: 217564

Background:
In response to DO3's consult request dated March 30, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and Carton/Container Labeling for the original application for FRUZAQLA™ (fruquintinib) capsules, for oral use. With this submission, the Applicant proposes an indication for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling sent by electronic mail to OPDP on September 19, 2023, and our comments are included below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling sent by electronic mail to OPDP on September 19, and we have no additional comments at this time.

Thank you for your consult. If you have any questions, please contact Andrew Nguyen at 240-402-0512 or andrew.nguyen@fda.hhs.gov.

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/s/

ANDREW D NGUYEN
10/02/2023 11:25:32 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 28, 2023
To:	Craig Long, PharmD Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Andrew Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FRUZAQLA (fruquintinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 217564
Applicant:	Takeda Pharmaceuticals USA, Inc.

1 INTRODUCTION

On March 30, 2023, Takeda Pharmaceuticals USA, Inc. submitted for the Agency's review an original New Drug Application (NDA) 217564 for FRUZAQLA (fruquintinib) capsules, for oral use. With this submission, the Applicant proposes an indication for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on March 30, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for FRUZAQLA (fruquintinib) capsules.

2 MATERIAL REVIEWED

- Draft FRUZAQLA (fruquintinib) capsules PPI received on March 30, 2023, and received by DMPP and OPDP on September 20, 2023.
- Draft FRUZAQLA (fruquintinib) capsules PI received on March 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 19, 2023.
- Approved STIVARGA (regorafenib) tablets, RETEVMO (selpercatinib) capsules, and COMETRIQ (cabozantinib) capsules comparator labeling December 10, 2020, September 21, 2022, and August 23, 2023, respectively.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

3 CONCLUSIONS

The PPI is acceptable with our recommended changes.

4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
09/28/2023 01:24:46 PM

ANDREW D NGUYEN
09/28/2023 02:17:58 PM

LASHAWN M GRIFFITHS
09/28/2023 02:41:03 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 26, 2023
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 217564
Product Name, Dosage Form, and Strength:	Fruzaqla (fruquintinib) Capsules, 1 mg and 5 mg
Applicant Name:	Takeda Pharmaceuticals USA, Inc
TTT ID #:	2023-4350-1
DMEPA 2 Safety Evaluator:	Ngoc-Linh Do, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling, received on September 13, 2023 for Fruzaqla. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Fruzaqla (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented our recommendations, however they added additional proposed revisions to the container labels and carton labeling after the applicant accepted the transfer of ownership of this NDA. We determined that the revised container label and carton labeling can be improved from a medication error perspective. Our comments for Takeda Pharmaceuticals are provided in Section 3 below.

3 RECOMMENDATIONS FOR TAKEDA PHARMACEUTICALS USA, INC

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

[a] Do, N. Label and Labeling Review for Fruzaqla (NDA 217564). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUL 26. TTT ID No.: 2023-4350.

A. General Comments (Container labels & Carton Labeling)

1. The net quantity statement is in close proximity to the product strength. We recommend relocating the net quantity statement away from the strength, such as to the bottom left side, adjacent to "Takeda". In addition, remove the word (b) (4) from the net quantity statement.

2. We recommend removing the statement (b) (4) as it is not necessary for capsules that are intended for oral use.

3. We recommend including the statement "Swallow capsules whole" on the PDP to align with the Prescribing Information, Section 2.1.

B. Carton Labeling

1. Remove the text (b) (4) in the Dosage statement. The statement should read "See Prescribing Information".

2. The net quantity statement is only required on the Principal Display Panel (PDP), (b) (4) We recommend removing the (b) (4)

3. Clarify the intent of the barcode displayed above the proprietary name on the PDP. If it is a 2D data matrix barcode, we recommend moving the barcode to the same panel as the Expiration and Lot number placement holder. If it not a 2D data matrix barcode, we recommend moving it to one of the side panels.

4. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder to the carton labeling.

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/s/

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09/27/2023 09:45:40 AM

ASHLEIGH V LOWERY
09/27/2023 09:48:08 AM

Clinical Inspection Summary

Date	September 18, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Michael Fusco, Clinical Analysis Sandra Casak, Team Leader Steven Lemery, MD, Division Director Division of Oncology 3 (DO3), Office of Oncology Products
NDA #	NDA 217564
Applicant	Takeda Pharmaceuticals International AG (Hutchmed Ltd)
Drug	Fruquintinib (HMPL-013)
NME (Yes/No)	Yes
Therapeutic Classification	Kinase Inhibitor
Proposed Indication(s)	Treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if RAS wild-type, an anti-EGFR therapy
Consultation Request Date	January 27, 2023
Summary Goal Date	September 30, 2023
Action Goal Date	November 29, 2023
PDUFA Date	November 30, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 2019-013-GLOB1 (FRESCO-2) were submitted to the Agency in support of New Drug Application (NDA 217564) for fruquintinib for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if RAS wild-type, an anti-EGFR therapy. Three clinical investigators (CIs), Drs. Sara Lonardi (site # 17090), Howard Hochster (site # 41060), and Nageshwara Arvind Dasari (site # 41020), as well as the Contract Research Organization (CRO), (b) (4), were inspected.

Inspections of the CIs, Drs. Lonardi, Hochster, and Dasari, as well as the CRO (b) (4) revealed no discrepancies or regulatory violations. Based on these inspections, Study FRESCO-2 appears to have been conducted adequately and the data generated by the inspected CIs and the CRO appear acceptable in support of the proposed indication.

Of note, the inspection results of Dr. Hochster are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Hutchmed International Corporation submitted NDA 217564 seeking approval for fruquintinib for use in patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if RAS wild-type, an anti-EGFR therapy.

The NDA is supported by the efficacy and safety data from Study 2019-013-GLOB1 (FRESCO-2) which is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 clinical trial to compare the efficacy and safety of fruquintinib in combination with best supportive care (BSC) versus placebo in combination with BSC in patients with mCRC who had progressed on or were intolerant to chemotherapy, biologics, and TAS-102 and/or regorafenib. Eligible subjects were randomly assigned in a 2:1 ratio to receive either fruquintinib 5 mg PO QD or placebo 5 mg PO QD for 3 weeks of continuous dosing followed by a 1-week break. The primary efficacy endpoint of FRESCO-2 study was overall survival (OS). Key secondary endpoints were progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) as assessed by the investigator according to RECIST v1.1.

Efficacy data from 691 randomized subjects (461 in the fruquintinib arm and 230 in the placebo arm) were submitted to support the current NDA. Subjects were to sign the informed consent form before any study-specific procedures were to be performed. Imaging assessments were to be performed at baseline and every 8 weeks until progressive disease, death, new anticancer treatment, or study completion, whichever occurred first.

Study FRESCO-2 was ongoing at the time of NDA submission. The first subject was randomized on August 14, 2020. The data cut-off date for FRESCO-2 was July 29, 2022. Subjects were randomized across 124 clinical sites across Europe, Japan, Australia, and the United States. A total of 121 out of 691 subjects (17.5%) were enrolled across 30 sites in the US.

Drs. Sara Lonardi (site # 17090), Howard Hochster (site # 41060), and Nageshwara Dasari (site # 41020), as well as the CRO, (b) (4), were inspected.

III. RESULTS (by site):

1. **Dr. Sara Lonardi (Site # 17090)**
   Istitute Oncologico Veneto
   1 Via Gattamelata 64
   Padua, 35128 Italy

   Inspection dates: June 19 – June 23, 2023

   Dr. Lonardi was inspected as a routine PDUFA inspection for Study FRESCO-2. This was the first FDA inspection of this investigator.

   The site screened 68 subjects and randomized 52 subjects in FRESCO-2. Of the 52 subjects enrolled, 51 subjects had died, and one subject was on follow-up at the time of the inspection. A total of 42 subjects completed study treatment as planned.

   The inspection verified informed consent forms, inclusion/exclusion criteria, serious AEs, and efficacy data for all 52 subjects randomized at the site. In addition, non-serious AEs, protocol deviations, electrocardiogram assessment and safety monitoring were reviewed in 15 out of 52 subjects enrolled. Records were compared with data listing tables submitted to the NDA and no discrepancies were noted.

   Efficacy endpoint assessment consisted of verification of subject's survival status in the source records compared with the data submitted to the NDA. No discrepancies were found.

   Additional records reviewed include, but were not limited to, investigator agreements, financial disclosures, staff qualifications, Ethics Committee submissions and approvals, staff training, enrollment, delegation, and monitoring logs, and drug accountability.

   Based on the results of the inspection, data generated at Dr. Lonardi's site appear acceptable in support of the proposed indication in the NDA.

2. **Dr. Howard Hochster (Site # 41060)**
   Rutgers Cancer Institute of New Jersey
   195 Little Albany St
   New Brunswick, New Jersey 08903

   Inspection dates: August 14 – August 18, 2023

   The official establishment inspection report (EIR) is pending. The review below is from the summary close out email and communications with the inspector during the inspection. This report will be updated after review of the official EIR, if relevant additional information is included.
   Dr. Hochster was inspected as a routine PDUFA inspection for Study FRESCO-2. Dr.

Hochster was previously inspected in December 2003.

At the time of the inspection, the site had screened 13 and enrolled 9 subjects in the study. Of the 9 subjects enrolled at the site, all had discontinued from study treatment at the time of the data cut-off: one subject (ID # (b) (6)) died due to an AE of biliary obstruction, and 8 discontinued due to disease progression. At the time of the data cut-off, a total of 6 subjects had died (ID # (b) (6), (b) (6)), and 3 subjects remain in survival follow-up (ID # (b) (6)).

Source records for all 9 subjects were reviewed and compared with line listings submitted to the NDA. Records reviewed for informed consent documents, eligibility criteria, adverse events reporting, primary endpoint data, protocol deviations, clinical assessments, and laboratory reports. There was no evidence of under-reporting of AEs or protocol violations.

Imaging scans were performed according to the protocol and assessments were found to be consistent with data provided in the NDA. No significant deficiencies were observed.

Additional records reviewed during the inspection included, but were not limited to, financial disclosures, protocols and amendments, IRB approvals, sponsor's monitoring, and case report forms. No issues were identified.

Based on the results of the inspection, the FRESCO-2 study data generated at Dr. Hochster's site appear acceptable in support of the proposed indication in the NDA.

3. **Dr. Nageshwara Arvind Dasari (Site # 41020)**
MD Anderson cancer Center
1515 Holcombe Blvd
Houston, Texas 77030

Inspection dates: July 17 – July 20, 2023

Dr. Dasari was inspected as a routine PDUFA inspection for Study FRESCO-2. Dr. Dasari was previously inspected in October 2014.

At the time of the inspection, the site screened 19 subjects and enrolled 12 subjects in the study. One subject withdrew consent, one discontinued study treatment due to an adverse event and, 10 discontinued due to disease progression.

Source records for all 12 subjects enrolled at the site were reviewed. The inspection covered informed consent forms, physician notes regarding screening, eligibility criteria, progress notes, adverse events, laboratory reports, concomitant medications, and protocol deviations. No deficiencies were noted.

The primary efficacy endpoint was verifiable by comparing the survival status in the source records with the data submitted to the NDA. In addition, imaging reports from scans performed per protocol were reviewed and compared with the data listings for all target and non-target lesions for all subjects. No discrepancies were found.

Additional records reviewed included, but were not limited to IRB approvals, monitoring and communications with the sponsor, staff training, delegation logs, and financial disclosure.

Based on the results of the inspection, data generated at Dr. Dasari's site appear acceptable in support of the proposed indication in the NDA.

4. (b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as data audit and surveillance inspection for Study FRESCO-2. This inspection assessed (b) (4) oversight responsibilities for FRESCO-2 study as the CRO for the NDA Sponsor, Hutchmed Ltd. (b) (4) was previously inspected in (b) (4).

Documents reviewed during the inspection included, but not limited to FRESCO-2 study documents, data management plans, data collection and handling procedures, safety reporting and handling, selection of clinical site investigators and monitors, data monitoring committee activities, investigational product disposition, and vendor, contract, and service agreements. No issues were identified.

The inspection reviewed the records of the 3 sites selected for inspection: Drs. Sara Lonardi (site # 17090), Howard Hochster (site # 41060), and Nageshwara Dasari (site # 41020). Records reviewed included IRB approvals, financial disclosures, FDA 1572s, investigators agreements, monitoring visit reports and visit logs. Review of the site visits found that (b) (4) monitoring of the sites was conducted in accordance with the monitoring plan for the study.

Overall, (b) (4) oversight of the study and the CIs appeared adequate, as appropriate actions were taken with all issues identified during oversight activities. There were no issues with the staff qualifications, training, experience, or compliance with the investigational plan. The inspection did not observe issues related to safety/adverse event reporting for Study FRESCO-2.

Based on the results of the inspection, (b) (4) oversight, and monitoring of Study FRESCO-2, as the CRO for Hutchmed Ltd., appeared adequate.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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DARRTS: NDA 217564
Review Division /Project Manager/Craig Long
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

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MICHELE B FEDOWITZ
09/18/2023 10:13:17 AM

JENN W SELLERS
09/18/2023 10:40:44 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217564
Submission Number	0003
Submission Date	3/30/2023
Date Consult Received	5/1/2023
Drug Name	Fruquintinib (HMPL-013)
Indication	Treatment of patients with metastatic colorectal cancer
Therapeutic Dose	5 mg QD for 21 days followed by 7 days off-treatment
Clinical Division	DO3
Protocol Review	Link

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

This review responds to your consult dated 5/1/2023 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND 131038 dated 02/12/2020 in DARRTS;
- Protocol version 1 for study 2019-013-GLOB1 (NDA 217564 / eCTD 0003; link);
- Study report for study 2019-013-GLOB1 (NDA 217564 / eCTD 0003; link);
- QT evaluation report (NDA 217564 / eCTD 0003; link);
- Concentration-QTc report (NDA 217564 / eCTD 0003; link);
- Investigator's brochure (NDA 217564 / eCTD 0003; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 217564 / eCTD 0003; link)
- Labeling (link)

1 SUMMARY

Fruquintinib does not cause mean QTc interval prolongation ≥ 20 msec based on the results of Study 2019-013-GLOB1 (FRESCO-2) – see Table 1 for results. Without a positive control or a large exposure margin, we are reluctant to conclude that fruquintinib has no effect on QTc (E14 Q&A 6.1).

FRESCO-2 was a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study to compare the efficacy and safety of fruquintinib plus best supportive care (BSC) to placebo plus BSC in patients with refractory metastatic colorectal cancer (mCRC), randomized in a 2:1 ratio to the fruquintinib group versus the placebo group. Patients were administered fruquintinib 5 mg QD or placebo for 3 weeks on and 1 week off (3w/1w), in a 28-day cycle (Proposed therapeutic dosage regimen). The steady state

mean fruquintinib Cmax (300 ng/mL) is similar to that observed (291 ng/mL) in study 2015-013-00US1, a clinical study using the same dosing regimen. The anticipated high clinical exposure for fruquintinib is the same as the clinical exposure. However, the steady state mean M11 (metabolite) Cmax covers only 0.50-fold of high clinical Cmax for the metabolite (2.3-fold increase with concomitant strong CYP3A4 inducers).

Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that fruquintinib is associated with large mean increases (≥ 20 msec) in the QTcF interval (refer to section 4.5). The findings of the primary analysis are further supported by the lack of QTc prolongation in by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• The high clinical scenario is the same as the clinical scenario. The maximum tested dose is 5 mg once daily for 3 weeks on and 1 week off (3w/1w), in a 28-day cycle. This is also the recommended dose in USPI.
• The steady state Cmax of the clinical trial dosing regimen (5 mg QD, 3w/1w, the recommended dose) is 291 ng/ml and the highest dose in the QT assessment provided steady state Cmax of 300 ng/ml (Cmax ratio ≈ 1 for fruquintinib).
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Period Day (C)</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>Fruquintinib</td><td>1</td><td>105.5 ng/ml</td><td>-2.2</td><td>(-4.5 to 0.0)</td></tr>
<tr><td>ΔΔQTcF</td><td>Fruquintinib</td><td>21</td><td>299.6 ng/ml</td><td>1.6</td><td>(-1.4 to 4.7)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">• Integrated nonclinical risk assessment was not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

The highest and only dose of 5 mg QD 3w/1w in the QT study (2019-013-GLOB1) does not cover high clinical Cmax for the metabolite, and further, the highest dose does not provide ≥ 2-fold high clinical exposure coverage to waive a positive control. Therefore,

although the upper bound of model-predicted ΔΔQTc is < 10 msec (4.7 msec), fruquintinib's QT effects is evaluated under ICH E14 Q&A 6.1. Specifically, ICH E14 Q&A 6.1 allows for excluding large QT effects (≥ 20 msec) of a drug if it does not prolong the QT interval by >10 msec without a positive control.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0003 (link) from the CSS-IRT.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling" draft guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Fruquintinib (HMPL-013) is a tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 that is proposed for the treatment of patients with metastatic colorectal cancer, who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. The proposed dose is 5 mg QD for 21 days followed by 7 days off for each 28-day cycle.

We previously agreed to the proposal to characterize the effects on the QTc interval in the proposed Phase 3 study (2019-013-GLOB1) using concentration-QTc analysis. The proposal was to collect ECG/PK on days 1 and 21 of cycle 1 (pre-dose, 1, 2, 3 and 4 h)

and at 2 h post-dose in cycles 2 and 3 on day 21 (safety ECGs) in 80 patients on fruquintinib and 40 patients on placebo. However, we noted that the sponsor should describe the subgroup enrollment criteria and we expressed concerns about treatment-group differences in background therapy, which might include QTc prolongers. (DARRTS 02/12/2020) The study protocol notes that the first 120 enrolled patients will be included into the QTc subgroup. Notably, study 2019-013-GLOB1 excludes patients receiving concomitant QTc prolonging medication and prohibits concomitant administration of drugs associated with QTc prolongation.

The primary analysis is concentration-QTc with by-time as supportive analysis in all patients with Holter ECGs collected in triplicate at baseline and post-baseline, and patients with ECG and concentrations taken <30 minutes apart. Same subjects will be included in categorical analysis.

3.1.1 Clinical pharmacology

The sponsor Hutchmed International Corporation is developing Fruquintinib (HMPL-013), a vascular endothelial growth factor (VEGF)-receptor kinase inhibitor, for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF (vascular endothelial growth factor) therapy; and, in RAS ('rat sarcoma') wild-type, and anti-epidermal growth factor receptor (EGFR) therapy. Fruquintinib is a highly selective and potent tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGF) receptors -1, -2 and -3. Its mechanism of action indicates that it will not affect cardiac channels.

Drug Product and Dosing Information: Fruquintinib (HMPL-013, MW: 393.39 g/mol) is a small molecule and the dosage form is 1 mg and 5 mg capsules. The sponsor mentions that the same capsule formulation has been used during clinical development and will remain the same commercially.

The recommended dose is 5 mg administered orally once daily without regard to food for the first 21 days (3 weeks) followed by 1 week off (3 weeks on/1 week off [3/1]) therapy on a 28-day treatment cycle for each 28-day cycle.

Pharmacokinetics: See the highlights of clinical pharmacology for Pharmacokinetics information (link). The two main features are (a) race has no effect on fruquintinib exposure (see Reviewer's Comment below related to exposure) and (b) from a Cmax standpoint the CYP3A inducer Rifampin decreases fruquintinib Cmax by 12 % but increases Cmax of the metabolite M11 by 2.3-fold (see Reviewer's Comment below).

Reviewer's Comment: The increase in the Cmax of M11 (metabolite) by 2.3-fold should be looked at with totality also considering the effect of rifampin on the AUC of the two moieties, i.e., the parent drug and the metabolite M11. It should be noted that M11 is 10-fold less potent against VEGFR-2 compared to fruquintinib and it has no meaningful contribution to the overall pharmacological activity of fruquintinib. Rifampin decreased the AUC of fruquintinib (parent drug) by 65 % but had no effect on the AUC of M11. The decrease in the AUC of fruquintinib is considerable. The sponsor mentions in the Labeling to avoid concomitant use of drugs that are strong or moderate CYP3A inducers with fruquintinib.

Overall, there is exposure coverage for this oncology drug fruquintinib for metastatic colorectal cancer.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	5 mg QD, oral tablets	- Fruquintinib: 291 ng/mL (Cmax,ss) - *M11: 77.4 ng/mL (Cmax,ss)
Sponsor's High clinical exposure scenario	- Severe hepatic: Impact on fruquintinib PK is unknown - 2.3-fold increase in M11 Cmax,ss with strong CYP3A4 induction	- Fruquintinib: 291 ng/mL (Cmax,ss) - M11: 177.1 ng/mL
Highest dose in QT assessment	5 mg QD, oral tablets	[a]Fruquintinib: 299.6 ng/mL [b]M11: 89.6 ng/mL
C_{max} Ratio	Fruquintinib: 299.6 / 291 = 1.02 M11: 89.6/177.1 = 0.50	

[a]Fruquintinib geometric mean Cmax calculated from the final qtpk_analysis dataset prepared by FDA. Note that the sponsor reported geometric mean Cmax of 278 ng/ml in Clinical Study Report: List of tables, Table 14.3.4.5.1. [b]M11 geometric mean Cmax calculated from the final qtpk_analysis dataset prepared by the FDA. Note that the sponsor reported arithment mean of 91.8 ng/ml in Tables 14.3.4.6.1. *This value is presented in the summary of clinical pharmacology studies, Table 28.

3.1.2 Nonclinical Safety Pharmacology Assessments

The IC_{50} of fruquintinib on hERG was > 13.08 µM (> 5,146 ng/mL), which is >378-fold greater than the unbound human C_{maxSS} at the proposed clinical dose of 5 mg QD 3/1 of fruquintinib (total concentration, approximately 290 ng/mL; unbound concentration based on protein binding of 95.3%, 13.6 ng/mL).

The IC_{50} of M11 (HM5025423) on hERG was > 6.05 µM (> 2,295 ng/mL), which is > 1000-fold greater than the unbound human C_{maxSS} for M11 at the proposed clinical dose of 5 mg QD 3/1 of fruquintinib (total concentration, approximately 77 ng/mL; unbound concentration based on protein binding of 97.7%, 1.77 ng/mL).

Reviewer's comment: *The hERG assays showed deviations (i.e., hERG current was recorded at a slower stimulating rate of every 15 s; lack of hyperpolarized pulse to assess the input resistance; lack of a full blocker at the end of the experiment to determine the non-hERG current) from the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1. The results showed that fruquintinib and M11 inhibited the hERG current by 2.6% and 8.6%, at concentrations of 13.08 µM and 6.05 µM, respectively. The hERG safety margins of fruquintinib and the major metabolite M11 are summarized below:*

Table *3. Safety Margins of fruquintinib and M11 on hERG Current*

Drug	*Cmax (ng/mL)*	*Protein Binding*	*Free Cmax (ng/mL)*	*hERG IC50 (μM)*	*Mol Weight (g/mol)*	*Safety Margin (Ratio)*
Fruquintinib	*281*	*95.3%*	*13.2*	*>13.08 (2.6% inhibition)*	*393.4*	*>390 x*
HM5025423(M11)	*77*	*97.7%*	*1.77*	*>6.05 (8.6% inhibition)*	*379.3*	*>1297x*

The hERG assay results showed that the safety margins of fruquintinib and the major metabolite M11 are > 390x (2.6% inhibition at 13.08 μM) and > 1297 x (8.6% inhibition at 6.05 μM), respectively, suggesting that fruquintinib and metabolite M11 have low risk for QT prolongation by directly inhibition the hERG current at anticipated clinical exposure. The limitations of the hERG assay are not expected to impact the large hERG safety margins.

Safety pharmacology study in anesthetized Beagle dogs at doses up to 0.34 mg/kg single dose and the collected ECGs in the 4-, 13-, and 39-week repeat-dose toxicity studies in dogs (highest doses of 0.3, 0.12, and 0.2/0.12 mg/kg/day, respectively) did not reveal any fruquintinib-related changes in QTc.

Reviewer's comment: *The concentration of fruquintinib and M11 were lower in all in vivo QT studies compared to therapeutic exposures (fruquintinib: 281 ng/mL; M11: 77 ng/mL):*

- *Single dose: No PK results located.*
- *4-week repeat:*
  - *0.3 mg/kg/day (Day 1): 77 ng/mL (fruquintinib), M11 not quantified. Day 28 data not reported as 5/6 animals were found dead during dosing phase.*
- *13-week repeat:*
  - *0.12 mg/kg/day (Day 91): 105 ng/mL (fruquintinib) and 5 ng/mL (M11).*
- *39-week repeat:*
  - *0.12 mg/kg/day (Day 273): 130 ng/mL (fruquintinib, M11 not quantified*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for fruquintinib was based on exposure-response analysis, please see section 3.2.3 for additional details.

In the sponsor's by-time analysis, the upper bound of 90% CI of the least-squares mean ΔΔQTcP and ΔΔQTcF on cycle 1 day 21 were below 10 msec at all nominal times. Results on other ECG intervals were not included.

Reviewer's comment: *The results from the reviewers' default model also show maximum upper confidence limit below 10 msec. Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable

3.2.2 Categorical Analysis

Per sponsor's analysis, there was one significant outlier for QTc (i.e., >500 msec or >60 msec over baseline), eight outliers for HR (<50 beats/min with 25% below baseline or >100 beats/min with 25% over baseline), one outlier for PR (>200 msec and 25% over baseline), and one outlier for QRS (>120 msec and 25% over baseline).

Reviewer's comment: *Reviewer's categorical analyses included all subjects except ECG and concentrations taken >30 minutes apart subjects (13 subjects) and no Holter triplicate baseline subjects. Reviewer's analysis results are similar with sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

Linear mixed-effects modeling was used for the analysis with the ΔQTcP as the dependent variable. The sponsor mentions that the corrected QT interval using Fridericia's formula (QTcF) did not provide adequate heart rate correction of the QT interval. Therefore, a population-based corrected QT interval (QTcP) was derived using baseline (cycle 1 day 1 predose). Three sets of models were evaluated:

a) ΔQTcP versus fruquintinib concentrations (Akaike information criterion [AIC]=10754.72)

b) ΔQTcP versus M11 concentrations (AIC=10727.07)

c) ΔQTcP versus fruquintinib and M11 concentrations, with separate slopes estimated for fruquintinib and M11 (AIC=10728.75).

The model with M11 concentration had the lowest AIC and was selected as the final model.

Primary Analysis is C-QTc Analysis: The primary analysis was concentration-QTc analysis, and the model included intercept, treatment (fruquintinib versus placebo), nominal time, visit, and baseline QTcP terms, with independent between-subject variability on the intercept and ΔQTcP-M11 concentration slope.

Based on ΔQTcP: A statistically significant slope (95% CI) of 0.0339 (0.00516, 0.0625) msec per ng/mL (p=0.0212) was estimated.

The final model was used to generate predictions of ΔΔQTcP, and the upper bounds of the 90% CI of mean ΔΔQTcP at the Cmax of M11 (77 ng/mL) and twice the Cmax (154 ng/mL) were 0.0537 msec and 4.00 msec, respectively below the clinically significant threshold of 10 msec. The model predicts that the upper bound of the 90% CI of mean ΔΔQTcP will exceed 10 msec at an M11 concentration of 262 ng/mL (3.4-fold higher than the observed Cmax of M11) and the 20 msec threshold of concern if exceeded for oncology drugs at an M11 concentration of 437 ng/mL (5.7-fold higher than the observed Cmax of M11).

Because about 35 % of M11 concentrations were below the limit of quantification the sponsor also obtained predictions using the model that included *only* fruquintinib

concentrations. Results are comparable with the upper bound of the 90% CI of the predicted mean ΔΔQTcP at twice the GM steady state fruquintinib Cmax (580 ng/mL) was 3.96 msec.

Based on ΔQTcF: A supportive analysis was performed using change from baseline in the corrected QT interval using Fridericia's formula (ΔQTcF). The slope for ΔQTcF-M11 was 0.0477 (95 % CI 0.0158, 0.0795) msec per ng/mL (p=0. 0035).

The predicted upper bounds of the 90% CI of the mean ΔΔQTcF for the M11 Cmax and twice the M11 Cmax were 3.07 and 8.34 msec, respectively, and was predicted not to exceed 10 msec at M11 concentrations up to 177 ng/mL, 2.3-fold higher than the observed M11 Cmax at steady state.

ΔΔQTcF predictions based on the model with *only* fruquintinib concentrations predict an upper bound of the 90% CI mean ΔΔQTcF <10 msec at twice the GM steady-state Cmax of fruquintinib following fruquintinib 5 mg QD.

Reviewer's comment: *In contrast to the sponsor, the dependent variable in the reviewer's primary model was ΔQTcF and fruquintinib was the predictor variable. Consistent with the sponsor's findings, the results from the reviewer's analysis indicates that fruquintinib treatment is not associated with clinically significant QT prolongation at the recommended therapeutic dose regimen.*

3.2.4 Safety Analysis

A comprehensive dataset for TEAEs typically associated with Torsade de Pointes/QT prolongation (FDA, 2005) was pooled as per the ISS SAP in the 3 monotherapy ISAS sets listed in ISS Section 4.5.1.3. Torsade de Pointes/QT prolongation AEs are presented by PT and Common Terminology Criteria for Adverse Events (CTCAE) grade as shown in Table 4.

Reviewer's comment:

- ISAS-mCRC: All patients from the three randomized, placebo-controlled, double-blinded (2019-013-GLOB1, 2013-013-00CH1, and 2012-013-00CH1) who received a single dose of fruquintinib or placebo. This excludes patients from open-label lead-in of 2013-013-00CH1.
- ISAS Expanded-mCRC: All patients with metastatic colorectal cancer (mCRC) who received at least 1 dose of study drug at the same schedule as in FRESCO-2 (2019-013-GLOB1) and FRESCO-1 (2013-013-00CH1). This set also includes patients from 3 open-label studies (2009-013-00CH1, 2012-013-00CH3, and 2015-013-00US1) who received the same study drug schedule as in FRESCO-2.

There were no significant differences between treatment groups in the number of patients who had Torsade de Pointes/QT prolongation TEAEs with any CTCAE grade or with CTCAE grade ≥ 3. Overall, the majority of TEAEs identified did not occur in the presence of a prolonged QT interval and were not considered to be cardiac in nature.

Table 4: Summary of Torsade de Pointes/QT Prolongation Events

	ISAS—mCRC				ISAS—Expanded mCRC	
Preferred Term	**Fruquintinib 5 mg 3/1 (N = 781)**		**Placebo (N = 391)**		**Fruquintinib (N = 911)**	
	CTCAE Grade		CTCAE Grade		CTCAE Grade	
	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)	Any n (%)	≥ 3 n (%)
Patients with any Torsade de Pointes/ QT prolongation TEAE	9 (1.2)	5 (0.6)	5 (1.3)	4 (1.0)	14 (1.5)	6 (0.7)
ECG QT prolonged	5 (0.6)	1 (0.1)	2 (0.5)	1 (0.3)	8 (0.9)	1 (0.1)
Syncope	3 (0.4)	3 (0.4)	0	0	3 (0.3)	3 (0.3)
Sudden death	1 (0.1)	1 (0.1)	2 (0.5)	2 (0.5)	2 (0.2)	2 (0.2)
Ventricular arrythmia	0	0	0	0	1 (0.1)	0
Cardiac arrest	0	0	1 (0.3)	1 (0.3)	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = common terminology criteria for adverse events; ECG = electrocardiogram; ISAS = integrated safety analysis set; ISS = Integrated Summary of Safety; mCRC = metastatic colorectal cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

Notes: The term "3/1" means a dosing schedule of 3-week on/ 1-week off during each 28-day cycle.
AEs are coded using MedDRA version 25.0.
Unless otherwise specified, percentages are based on the number of patients in each group (ie, N).
Patients with more than 1 TEAE were counted once at the worst severity category.
A patient with multiple TEAE entries in the same AESI category (PT) was only counted once within a particular AESI category (PT).
Number (%) of patients with TEAE, sorted by AESI category followed by PT in decreasing order of frequency (by Expanded mCRC, Any Grade column). If the frequencies tie, alphabetic order is applied.

Source: Table ISS,.5.3.2.16.2

Source: QT evaluation report, Table 8

Three fruquintinib-treated patients experienced nonserious AEs of syncope (details of these cases are described in Table 9). These patients had normal QTcF at baseline. Two of these patients experienced syncope secondary to concurrent AEs of hematochezia (1 patient) and dehydration (1 patient), respectively. One of these patients additionally experienced a nonserious AE of cardiac insufficiency secondary to Grade 2 kidney failure and fluid overload.

Reviewer's comment: *Review of patient narratives for the two patients that died suddenly and received fruquintinib, did not reveal QTc > 450 msec or other AEs related to TdP or QT. The ventricular arrhythmia (grade 1) was in a patient with occasional premature ventricular contractions that day and with all reported QTc < 450 msec. Similarly, no QTc measurements greater than 450 msec were reported for any of the patients who experienced syncope.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to study drug assignment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not applicable

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. ECG and concentrations taken >30 minutes apart subjects (13 subjects) and no Holter triplicate baseline subjects are excluded.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for the fruquintinib treatment group. The maximum ΔΔQTcF values by period day are shown in Table 5.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

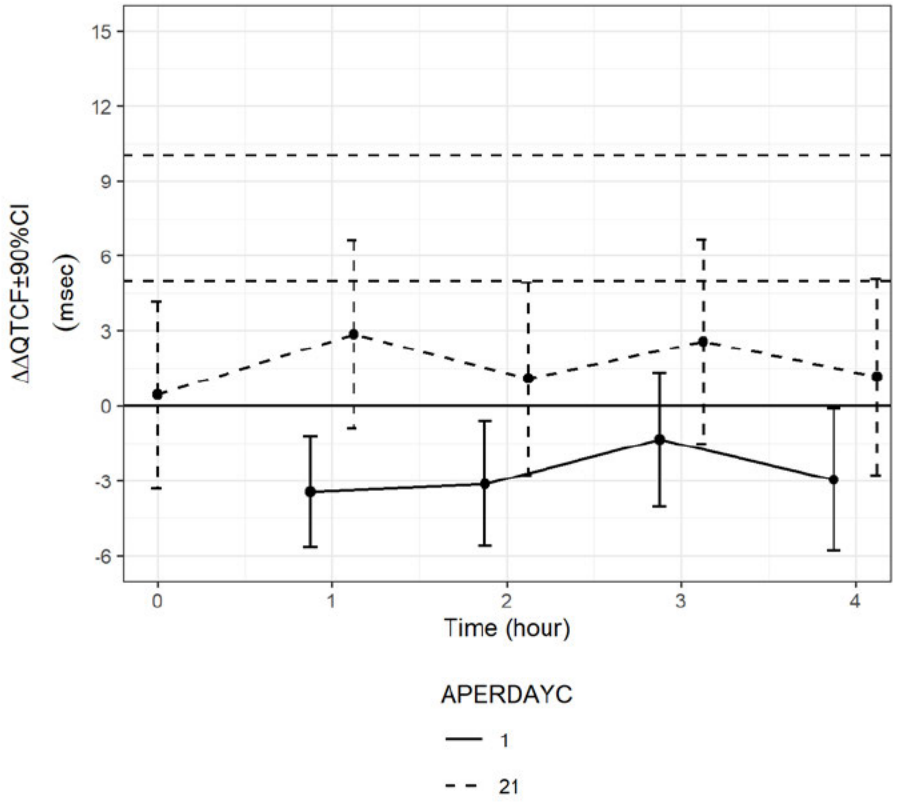


Table 5. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)
Fruquintinib_BSC	1	128 / 66	3.0	-1.3	(-4.0 to 1.3)
Fruquintinib_BSC	21	91 / 53	3.0	2.6	(-1.5 to 6.7)

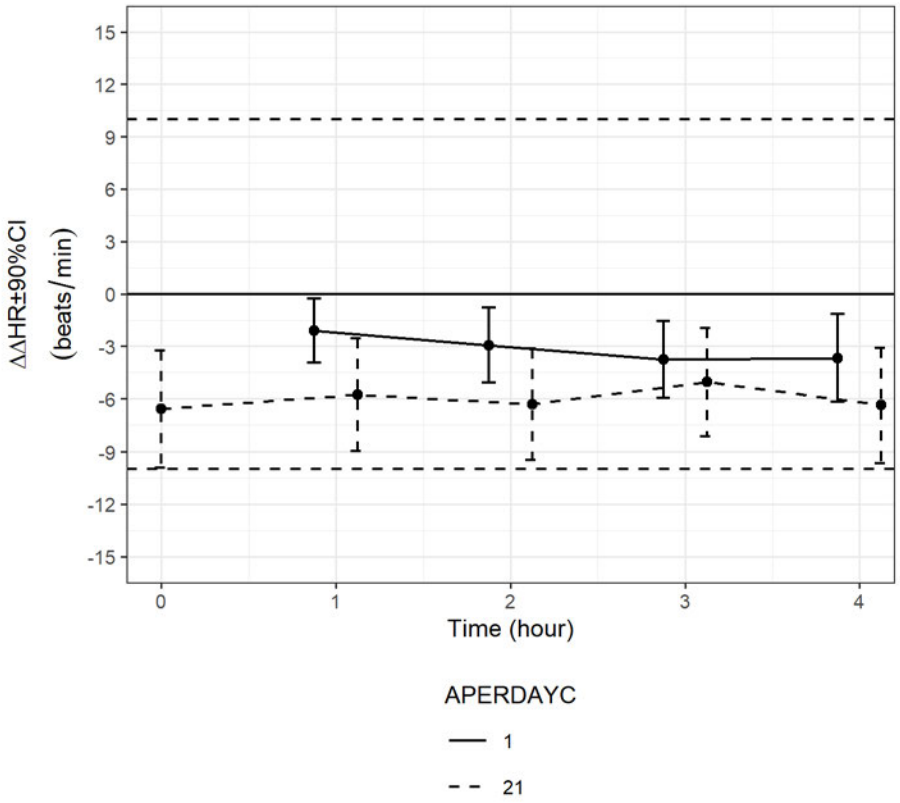
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for the Fruquintinib treatment group.

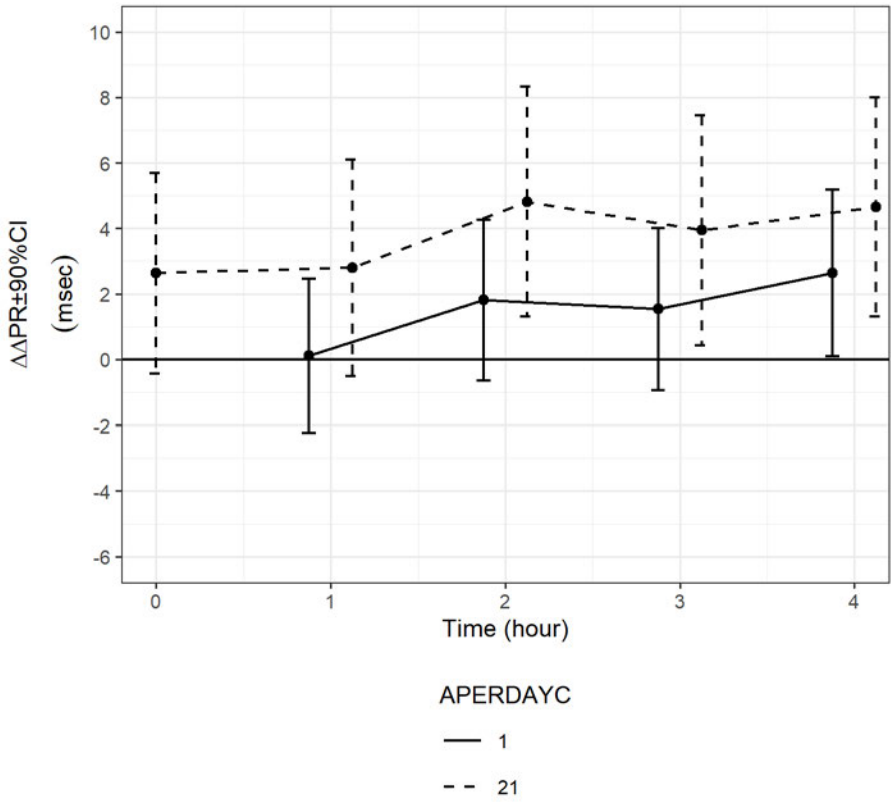
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for the Fruquintinib treatment group.

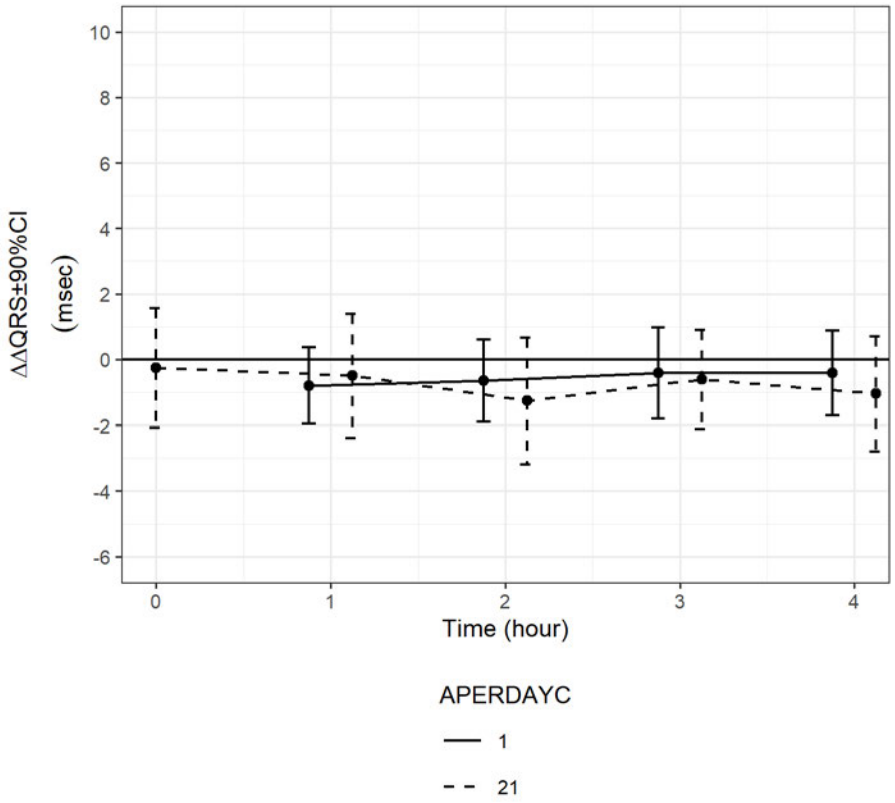
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for the Fruquintinib treatment group.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. ECG and concentrations taken >30 minutes apart subjects (13 subjects) and no Holter triplicate baseline subjects are excluded. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 6 lists the number of subjects, as well as the number of observations with QTcF values of ≤450 msec, >450 and ≤480 msec, >480 and ≤500 msec, and >500 msec with or without a change from baseline >60 msec. There was one subject who had observed QTc >600 msec without a change from baseline >60 msec in the fruquintinib treatment group.

Table 6: Categorical Analysis for QTcF (maximum)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & <=60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fruquintinib_BSC	131	957	117 (89.3%)	903 (94.4%)	10 (7.6%)	40 (4.2%)	3 (2.3%)	10 (1.0%)	1 (0.8%)	4 (0.4%)
Placebo	68	520	65 (95.6%)	509 (97.9%)	2 (2.9%)	7 (1.3%)	1 (1.5%)	4 (0.8%)	0 (0%)	0 (0%)

4.4.2 HR

Table 7 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min), and Table 8 lists the categorical analysis results for minimum HR (>45 beats/min and <45 beats/min). There were nine subjects having observed maximum HR above 100 beats/min in the fruquintinib treatment group. Three of them were 25% increase over baseline. There were four subjects having observed minimum HR below 45 beats/min in the fruquintinib treatment group. One of them was 25% decrease over baseline.

Table 7: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fruquintinib_BSC	131	958	122 (93.1%)	933 (97.4%)	9 (6.9%)	25 (2.6%)
Placebo	68	520	59 (86.8%)	495 (95.2%)	9 (13.2%)	25 (4.8%)

Table 8: Categorical Analysis for HR (minimum)

Actual Treatment	Total (N)		Value <=45 beats/min		Value >45 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fruquintinib_BSC	131	958	4 (3.1%)	13 (1.4%)	127 (96.9%)	945 (98.6%)
Placebo	68	520	0 (0%)	0 (0%)	68 (100.0%)	520 (100.0%)

4.4.3 PR

Table 9 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). There was one subject who had observed PR >220 msec with 25% increase over baseline in the fruquintinib treatment group.

Table 9: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fruquintinib_BSC	127	929	124 (97.6%)	920 (99.0%)	2 (1.6%)	8 (0.9%)	1 (0.8%)	1 (0.1%)
Placebo	66	501	64 (97.0%)	484 (96.6%)	2 (3.0%)	17 (3.4%)	0 (0%)	0 (0%)

4.4.4 QRS

Table 10 lists the categorical analysis results for QRS (≤120 msec, and >120 msec; with and without 25% increase over baseline). There was one subject who had observed QRS >120 msec with 25% increase over baseline in the fruquintinib treatment group.

Table 10: Categorical Analysis for QRS

Actual Treatment	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fruquintinib_BSC	131	957	121 (92.4%)	901 (94.1%)	9 (6.9%)	53 (5.5%)	1 (0.8%)	3 (0.3%)
Placebo	68	520	62 (91.2%)	477 (91.7%)	6 (8.8%)	43 (8.3%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

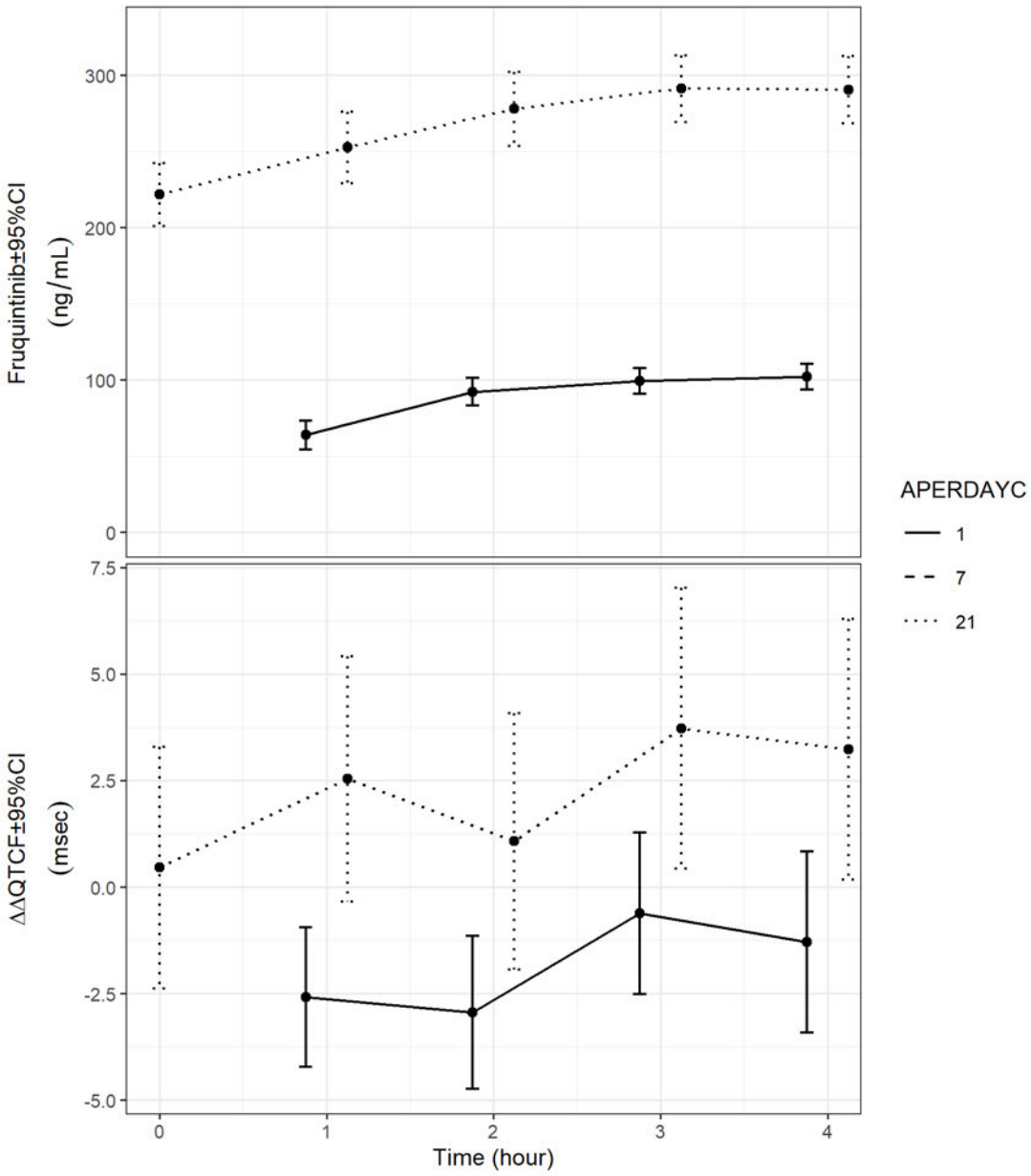
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

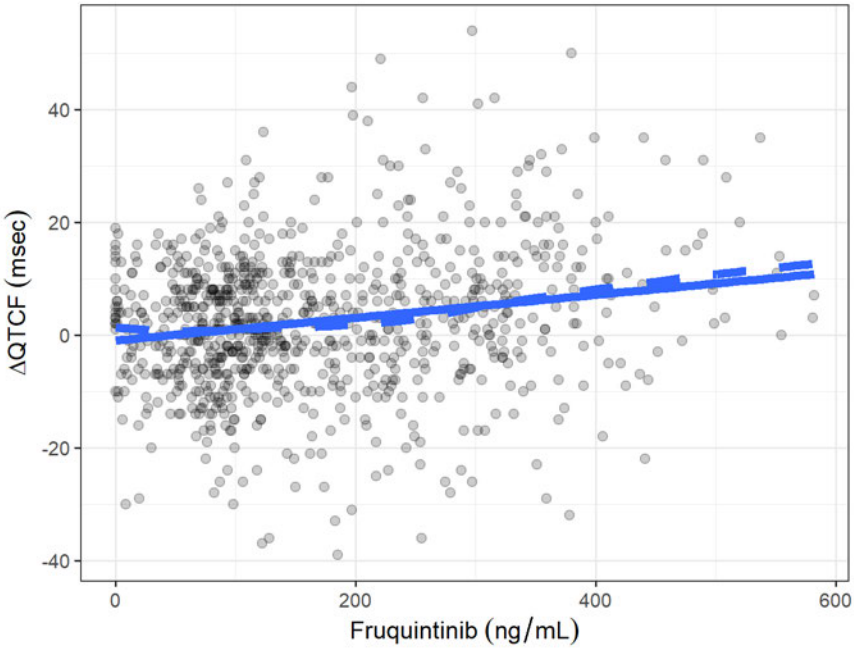
Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 11.

Figure 7: Goodness-of-fit Plot for QTcF

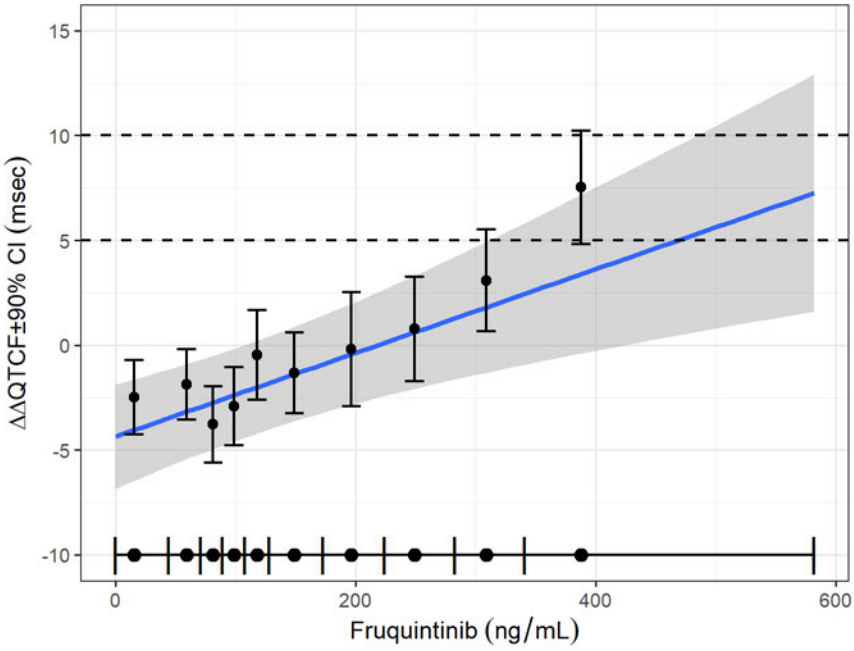


Table 11: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Fruquintinib (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Fruquintinib_BSC	1	105.5	-2.2	(-4.5 to 0.0)
Fruquintinib_BSC	21	299.6	1.6	(-1.4 to 4.7)

4.5.1.1 Assay Sensitivity

Assay sensitivity for Fruquinitinib was not established based on moxifloxacin. Instead, it is based on exposure margin using the integrated QT assessment pathway of 6.1 utilizing both clinical and non-clinical results.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

QT assessment plan previously reviewed (DARRTS 02/12/2020).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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 26, 2023
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 217564
Product Name, Dosage Form, and Strength:	Fruzaqla (fruquintinib) Capsules, 1 mg and 5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Hutchmed Limited
FDA Received Date:	March 30, 2023
TTT ID #:	2023-4350
DMEPA 2 Safety Evaluator:	Ngoc-Linh Do, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

As part of the approval process for Fruzaqla (fruquintinib) Capsules, the Division of Oncology 3 (DO3) requested that we review the proposed Fruzaqla patient package insert (PPI), prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters 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

We reviewed the proposed PPI, PI, container labels, and carton labeling and determined that they may be improved to promote the safe use of Fruzaqla from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI, container labels, and carton labeling that may be improved to increase readability and prominence of important information and promote safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Dosage and Administration Section, Section 2.1: Recommended Dose

a. We recommend moving the sentence, "Swallow the [TRADENAME] capsule whole. (b) (4), to a new paragraph so that this statement is more prominent.

b. For clarity, we recommend revising the sentence, "Take a missed dose if less than 12 hours have passed since the missed scheduled dose" to "Do not take a missed dose of Fruzaqla within 12 hours of the next scheduled dose".

c. In addition, we recommend revising the sentence, (b) (4) to "Do not take an additional dose if vomiting occurs after taking [TRADENAME] but continue with the **next scheduled dose"**

2. How Supplied/Storage and Handling Section, Section 16: How Supplied/Storage and Handling
   a. A description of the dosage form is not included in this section. We recommend including a description of identifying characteristics of the dosage form as required in accordance with 21 CFR 201.57(c)(17)(iii).
   b. As currently presented, the storage temperature is stated as (b) (4) (b) (4) Typically, the storage temperature is provided as a range. For accuracy of the storage temperature, we defer to CMC.

4.2 RECOMMENDATIONS FOR HUTCHMED LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. Delete (b) (4) after the product strength to minimize redundancy as the dosage form is included next to the established name.
2. (b) (4)
3. Revise the temperature to state "Store at 20°C to 25°C (68°F to 77°F). Brief exposure to 15 °C and 30 °C (59 °F to 86°F) permitted (see USP Controlled Room Temperature)".
4. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on

the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

5. For Fruzaqla 1 mg container labels & carton labeling, the color contrast between the (b) (4) of the strength could be improved to ensure adequate readability. We recommend a (b) (4) or other means as needed to increase the prominence of the strength statement and improve readability.

B. Container Labels

1. The linear barcode is missing on the 1 mg and 5 mg container labels.
   The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).
   Add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fruzaqla received on February 30, 2023 from Hutchmed Limited.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Fruzaqla</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>fruquintinib</td></tr>
<tr><td>Indication</td><td>For the treatment of patients with metastatic colorectal cancer (mCRC)
who have been previously treated with fluoropyrimidine-, oxaliplatin-,
and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy</td></tr>
<tr><td>Route of Administration</td><td>Orally</td></tr>
<tr><td>Dosage Form</td><td>Capsules</td></tr>
<tr><td>Strength</td><td>1 mg and 5 mg</td></tr>
<tr><td>Dose and Frequency</td><td>5 mg orally once daily for the first 21 days followed by 7 days off treatment for each 28-day cycle. Continue treatment until disease progression or unacceptable toxicity occurs.

Dosage Modifications for Adverse Reactions
<table>
<tr><td>Dose Level</td><td>Fruzaqla (fruquintinib)</td></tr>
<tr><td>Recommended starting dose</td><td>5 mg orally once daily</td></tr>
<tr><td>First dose reduction</td><td>4 mg orally once daily</td></tr>
<tr><td>Second dose reduction</td><td>3 mg orally once daily</td></tr>
<tr><td colspan="2">Permanently discontinue Fruzaqla in patients unable to tolerate 3 mg orally daily.</td></tr>
</table></td></tr>
</table>

How Supplied	Fruzaqla 1 mg and 5 mg capsules are supplied as follows: • (b) (4) 21 capsules of Fruzaqla 1 mg in a bottle within a carton. The capsules are White to off-white powder filled into a size 3 hard gelatin capsule with standard yellow opaque cap and white opaque body, imprinted with “HM013” over “1mg” on the body in black ink. • (b) (4): 21 capsules of Fruzaqla 5 mg in a bottle within a carton. The capsules are White to off-white powder filled into a size 1 hard gelatin capsule with (b) (4) opaque cap and white opaque body, imprinted with “HM013” over “5mg” on the body in black ink.
Storage	(b) (4)
Container Closure	The primary packaging is a high-density polyethylene (HDPE) bottle with a (b) (4) child-resistant closure and an induction-sealed aluminum liner. Each bottle contains 21 capsules and a desiccant cartridge containing 1 g of silica gel. The bottle is packaged in a carton with an insert and sealed with a tamper-evident seal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 26, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘Fruzaqla’, ‘fruquintinib’, ‘IND 131038’, and ‘NDA 217564’. Our search identified one previous reviews[a], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Fruzaqla labels and labeling submitted by Hutchmed Limited.

[a] Do, N. Label and Labeling Review for Fruzaqla (fruquintinib (IND 131038 and NDA 217564). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 30. TTT ID No.: 2022 – 1044724707, 2023 – 1044725024

- Container label received on February 30, 2023
- Carton labeling received on February 30, 2023
- Patient Package Insert received on February 30, 2023, available from \\CDSESUB1\EVSPROD\nda217564\0003\m1\us\114-labeling\114a-draft-label\fruquintinib-patient-package-insert-clean-word.docx
- Prescribing Information (Image not shown) received on February 30, 2023, available from \\CDSESUB1\EVSPROD\nda217564\0003\m1\us\114-labeling\114a-draft-label\fruquintinib-uspi-clean-word.docx

F.2 Label and Labeling Images

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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