

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219097Orig1s000

OTHER REVIEW(S)

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 12, 2024

TO: R. Angelo De Claro, M.D.
Director
Division of Hematologic Malignancies I (DHMI)
Office of Oncologic Diseases (OOD)
Office of New Drugs (OND)

FROM: Monica Javidnia, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Brian J. Folian, J.D.
Deputy Director
OSIS

SUBJECT: Review of Clinical Inspection of Kailash Cancer
Hospital and Research Centre (Site 252), Vadodara,
Gujarat, India

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study MW180013 (protocol number CBCC/2018/013, NDA 219097) conducted at Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India.

Objectionable conditions were found during the inspection, and Form FDA 483 was issued at the inspection close-out. Based on the inspection observations, exhibits, and the firm's response to Form FDA 483, for Kailash Cancer Hospital and Research Centre for study MW180013, OSIS recommends the review division considers the impact of missing COVID-19 assessments for subjects (b) (6), (b) (6), and (b) (6) on visit days 8, 9, 16, and 17.

2. Inspected Study**NDA 219097**

Study Number: MW180013
Study Title: "An open label, multicenter, balanced,

randomized, two-treatment, two-period, two-sequence, two-way crossover, multiple-dose, steady state, comparative oral bioavailability study of Imatinib Mesylate Oral Solution 400 mg/5 ml of [REDACTED] ^{(b) (4)} with Gleevec® (Imatinib mesylate) Tablets 400 mg of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, in adult human patients with Chronic Myeloid Leukemia and/or Gastrointestinal Stromal Tumors under fed condition”

Dates of study conduct: 11/12/2020 - 06/28/2021

Clinical site: Kailash Cancer Hospital and Research Center
Muniseva Ashram, Goraj, Waghodia, Vadodara-391760
Gujarat, India

3. Inspectional Findings

Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

OII investigator Humberto Z. Gomez inspected Kailash Cancer Hospital and Research Centre, Muniseva Ashram, Goraj, Waghodia, Vadodara-391760 Gujarat, India from September 11-14 and 16, 2024.

3.1 Previous Inspection

The previous OSIS inspection of Kailash Cancer Hospital and Research Center was conducted from January 07-10, 2019. At the conclusion of the inspection, Form FDA 483 was not issued. There was one discussion item about the sample collection log not including collection dates for each sample collected over a 24-hour period. The final classification was NAI. Similar items were not noted during the current inspection.

3.2 Current Inspection

The current inspection included auditing the following items:

- Study records, including informed consent forms, for 10/10 enrolled subjects
- Select standard operating procedures (SOPs)
- Protocol adherence
- Institutional Ethics Committee (IEC), submissions and approvals

- Test article accountability and storage
- Randomization
- Adverse events

3.3 Inspection findings

At the conclusion of the inspection, investigator Gomez observed objectionable conditions, and Form FDA 483 was issued to the clinical site. There were no discussion items. The Form FDA 483 observation (**Attachment 1**), the firm's response dated 10/04/2024 (**Attachment 2**), and my evaluation are presented below.

1 3.3.1 FDA 483 Observations

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, according to the protocol version 3.0, Covid-19 signs and symptoms should be evaluated at screening, treatment periods Day 1 to Day 17, End of Treatment, and at the Safety Follow-Up visit.

Specifically for the following subjects there was no source documentation indicating that the Covid-19 Assessment was completed according to the protocol version 3.0. for this specific BA/BE Clinical Trial.

- Subject (b) (6) (Day 1, Day 8, Day 9, Day 16, Day 17 and End of Treatment Visits).
- Subject (b) (6) (Day 8, Day 16, Day 17 and End of Treatment Visits).
- Subject (b) (6) (Day 8, Day 9, Day 16, Day 17 and End of Treatment Visits).
- Subject (b) (6) (Day 8, Day 9, Day 16, Day 17 and End of Treatment Visits).
- Subject (b) (6) (Day 8, Day 9, Day 16, Day 17 and End of Treatment Visits).
- Subject (b) (6) (Day 8, Day 9, Day 16, Day 17 and End of Treatment Visits).
- Subject (b) (6) (Day 8, Day 9, Day 16, Day 17, and End of Treatment Visits).
- Subject (b) (6) (Day 8).

Note: the observation lists subject numbers in the randomization number format (i.e., (b) (6)) rather than the subject number format (i.e., (b) (6)). I confirmed that the numbers in Observation 1 refer to subject numbers.

Firm's Response: The site acknowledged that COVID-19 assessments were performed for three subjects (b) (6), (b) (6) and (b) (6) for Days 8, 9, 16, and 17 (End of Treatment). The site filed deviations and reported the deviations to the IEC.

The site stated that COVID-19 assessments were performed for the other five subjects but filed in the subjects' Inpatient Department documents then transcribed into the subjects' electronic case report forms (eCRFs). The site provided the documentation for the five subjects and visits: (b) (6) (Day 1, Day 8, Day 9, Day 16, Day 17), (b) (6) (Day 8, Day 16, Day 17), (b) (6) (Day 8, Day 9, Day 16, Day 17), (b) (6) (b) (6), (Day 8, Day 9, Day 16, Day 17), and (b) (6) (Day 8).

The site stated they prepared a new SOP on documentation and provided training to their site personnel on the new SOP.

OSIS Evaluation: Per the study protocol (see sections 10.1 and 10.3), 'COVID-19 Signs and Symptoms' were to be assessed at each visit. Per protocol section 9.2, COVID-19 positivity may be discontinued from the study. Additionally, per protocol section 10.4, Day 17 is the end of treatment; they are not separate visits unless the subject is discontinued early.

Observation 1 lists Day 17 and 'End of Treatment' separately, but these are not separate study visits, unless a subject is discontinued early. Therefore, there were 29 COVID-19 assessments collectively for eight subjects unavailable for the investigator's review during inspection, rather than 36 assessments.

Following review of the assessment data provided in the firm's response as is described above, I confirmed that 3 subjects of the 8 subjects identified in Observation 1 did not have a COVID assessment performed. Specifically, there is no documentation that subjects (b) (6), (b) (6), and (b) (6) were assessed for COVID-19 on visit days 8, 9, 16, and 17.

Thus, the firm violated the protocol for subjects (b) (6), (b) (6), and (b) (6) on visit days 8, 9, 16, and 17 by not performing COVID-19 signs and symptoms. I recommend that the review division considers the impact of missing COVID-19 assessments for subjects (b) (6), (b) (6), and (b) (6) on visit days 8, 9, 16, and 17.

Attachments

Attachment 1: Form FDA 483

Attachment 2: Site's response to Form FDA 483

Monica Javidnia, Ph.D.
Pharmacokineticist

Draft: MJ 10/30/2024, 11/05/2024, 11/06/2024, 11/08/2024
Edit: MO 11/01/2024, 11/05/2024, 11/06/2024, 11/09/2024; JD
11/08/2024

OSIS File #: BE 10192

eNSpect Assignment ID: 243179
eNSpect OpID: 284486

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/s/

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11/12/2024 11:10:08 AM

BRIAN J FOLIAN
11/12/2024 11:44:57 AM

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)

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Date of This Review:	October 25, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219097
Product Name, Dosage Form, and Strength:	Imkeldi (imatinib) Oral Solution, 80 mg/mL
Applicant Name:	Shorla Pharma Ltd
FDA Received Date:	October 21, 2024
TTT ID #:	2024-8113-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Shorla Pharma Ltd submitted revised container label and carton labeling received on October 21, 2024 for Imkeldi. We reviewed the revised container label and carton labeling for Imkeldi (Appendix A) to determine if they are 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

Shorla Pharma Ltd implemented all of our recommendations and we have no additional recommendations at this time.

^a Kundreskas, J. Review of Revised Label and Labeling for Imkeldi (NDA 219097). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 04. TTT ID: 2024-8113-1.

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/s/

NICOLE F IVERSON on behalf of JODY K KUNDRESKAS
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10/25/2024 07:33:31 AM

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

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

Memorandum

Date: October 9, 2024

To: Matthew Sherdel, Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

From: Samia Alam, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for IMKELDI (imatinib oral solution)

NDA: 219097

Background:

In response to DHM1's consult request dated January 31, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for IMKELDI (imatinib oral solution).

PI/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 30, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed IFU, and comments were sent under separate cover on October 2, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on October 1, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Samia Alam at (240) 402-3695 or Samia.Alam@fda.hhs.gov.

Section	Statement from draft	Comment
HIGHLIGHTS WARNINGS AND PRECAUTIONS	Impairments Related to Driving and Using Machinery: Caution patients about driving a car or operating machinery. (5.13)	OPDP notes the HL for the approved labeling for competitor product Gleevec also has the statement "Reports of motor vehicle accidents have been received in patients receiving Gleevec". To prevent minimization of risk and to be consistent with the competitor label, we recommend also including this information in the HL for Imkeldi.
HIGHLIGHTS DRUG INTERACTIONS	CYP3A4 inducers: Avoid or increase imatinib dosage if unavoidable.(7.1)	OPDP notes the HL for approved labeling for competitor product Gleevec also has reference to sections 2.12 and 12.3. For consistency with the competitor label and to help guide the reader to additional information about this drug interaction, we recommend also including references to sections 2.12 and 12.3. We also note the HL for the approved labeling for competitor product Gleevec has the statement "CYP3A4 inducers may decrease Gleevec Cmax and area under curve (AUC)". We defer to DHM1 if this information should be included in the HL.
HIGHLIGHTS DRUG INTERACTIONS	CYP3A4 inhibitors: Use caution. Avoid grapefruit juice. (7.2)	OPDP notes the HL for approved labeling for competitor product Gleevec also has

		reference to section 12.3. For consistency with the competitor label and to help guide the reader to additional information about this drug interaction, we recommend also including reference to section 12.3. We also note the HL for the approved labeling for competitor product Gleevec has the statement “CYP3A4 inhibitors may increase Gleevec Cmax and AUC”. We defer to DHM1 if this information should be included in the HL.
HIGHLIGHTS DRUG INTERACTIONS	• CYP3A4 substrates: Use caution. Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin. (7.3) • CYP2D6 substrates: Use caution. (7.4)	OPDP notes the HL for approved labeling for competitor product Gleevec has the statement “Gleevec is an inhibitor of CYP3A4 and CYP2D6 which may increase the Cmax and AUC of other drugs”. We defer to DHM1 if this information should be included in the HL. Additionally, the HL for approved labeling for competitor product Gleevec also has reference to section 12.3. For consistency with the competitor label and to help guide the reader to additional information about these drug interactions, we recommend also including reference to section 12.3.
DRUG INTERACTIONS	Imatinib increases exposure of CYP3A substrates [see <i>Clinical Pharmacology (12.3)</i>], which may	OPDP notes the approved labeling for competitor product Gleevec provides

7.3 Interactions With Drugs Metabolized by CYP3A4	increase the risk of adverse reactions related to these substrates.	examples of CYP3A substrates (“e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc”). For consistency with the competitor label and to provide additional clarity, we suggest providing details on the CYP3A substrates.
USE IN SPECIFIC POPULATIONS 8.1 Pregnancy	Advise pregnant women of the potential risk to a fetus.	OPDP notes the approved labeling for competitor product Gleevec includes the statement “Advise women to avoid pregnancy when taking Gleevec.” For consistency with the competitor label and to prevent minimization of risk, we suggest also including this statement in the Imkeldi label.
USE IN SPECIFIC POPULATIONS 8.3 Females and Males of Reproductive Potential	Based on human postmarketing reports and animal studies, Imkeldi can cause fetal harm [see <i>Use in Specific Populations (8.1)</i>].	OPDP notes the approved labeling for competitor product Gleevec states “...<u>have shown</u> Gleevec to be harmful to the developing fetus” (underlined emphasis added). For consistency with the competitor label and to prevent minimization of risk, we suggest revising this statement.
CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics <i>Specific Populations</i> <u>Hepatic Impairment</u>	The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 patients with cancer and varying degrees of hepatic impairment at	OPDP notes the approved labeling for competitor product Gleevec has reference to section 8.6. For consistency with the competitor label and to help guide the reader to

	imatinib doses ranging from 100 mg to 800 mg.	additional information about use in patients with hepatic impairment, we recommend also including this reference for Imkeldi. Additionally, we note the approved labeling for Gleevec has the statement “Dose reductions are necessary for patients with severe hepatic impairment [see <i>Dosage and Administration (2.12)]</i>”. For consistency with the competitor label and to ensure safe use of Imkeldi, we also recommend including this statement.
CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics <u>Specific Populations</u> <u>Renal Impairment</u>	The effect of renal impairment on the pharmacokinetics of imatinib was assessed in 59 cancer patients with varying degrees of renal impairment at single and steady state imatinib doses ranging from 100 to 800 mg/day.	OPDP notes the approved labeling for competitor product Gleevec has reference to section 8.7. For consistency with the competitor label and to help guide the reader to additional information about use in patients with renal impairment, we recommend also including this reference for Imkeldi. Additionally, we note the approved labeling for Gleevec has the statement “Dose reductions are necessary for patients with moderate and severe renal impairment [see <i>Dosage and Administration (2.12)]</i>”. For consistency with the competitor label and to ensure safe use of Imkeldi, we also

		recommend including this statement.
CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics <i>Drug Interactions</i> <u>Agents Inducing CYP3A Metabolism</u>		OPDP notes the approved labeling for competitor product Gleevec has the statement “Gleevec doses up to 1,200 mg/day (600 mg twice daily) have been given to patients receiving concomitant strong CYP3A4 inducers [see <i>Dosage and Administration (2.12)】</i> ”. We defer to DHM1 if this information should be included.
CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics <i>Drug Interactions</i> <u>Agents Inhibiting CYP3A Metabolism</u>		OPDP notes the approved labeling for competitor product Gleevec also has the information “Caution is recommended when administering Gleevec with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided.” For consistency with the competitor label and to provide additional context regarding this drug interaction for safe use, we recommend including this information.
CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics		OPDP notes the approved labeling for competitor product Gleevec also has the information “Particular

<i>Drug Interactions</i> <u>Interactions with Drugs</u> <u>Metabolized by CYP3A4</u>		caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus, or tacrolimus). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low- molecular weight or standard heparin instead of warfarin.” For consistency with the competitor label and to provide additional context regarding this drug interaction for safe use, we recommend including this information.
CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics <i>Drug Interactions</i> <u>Interactions with Drugs</u> <u>Metabolized by CYP2D6</u>		OPDP notes the approved labeling for competitor product Gleevec also has the information “No dose adjustment is necessary, however, caution is recommended when administering Gleevec with CYP2D6 substrates that have a narrow therapeutic window.” For

		consistency with the competitor label and to provide additional context regarding this drug interaction for safe use to the reader, we recommend including this information.
CLINICAL STUDIES 14.1 Chronic Myeloid Leukemia <i>Chronic Phase, Newly Diagnosed:</i>	Table 18: Response in Newly Diagnosed CML Study (84-Month Data)	OPDP notes there is not a Table 16 or Table 17 in the FPI. Thus, we recommend revising this to Table 16 and revising the remainder of the tables in the FPI accordingly.
PATIENT COUNSELING INFORMATION <u>Embryo-Fetal Toxicity</u>	Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant [see <i>Warnings and Precautions (5.10) and Use in Specific Populations (8.1)</i>]. Advise females of reproductive potential to use effective contraception during treatment with Imkeldi and for 14 days after the last dose [see <i>Use in Specific Populations (8.3)</i>].	OPDP notes the approved labeling for competitor product Gleevec has the statement “Advise women of reproductive potential to avoid becoming pregnant while taking Gleevec”. For consistency with the competitor label and to prevent minimization of risk, we recommend also including this statement for Imkeldi.

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/s/

SAMIA ALAM
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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)

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Date of This Review:	October 4, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219097
Product Name, Dosage Form, and Strength:	Imkeldi (imatinib) Oral Solution, 80 mg/mL
Applicant Name:	Shorla Pharma Ltd
FDA Received Date:	September 18, 2024 and September 24, 2024
TTT ID #:	2024-8113-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Shorla Pharma Ltd submitted an Instructions for Use (IFU) received on September 18, 2024 for Imkeldi. Additionally, Shorla Pharma Ltd submitted revised container label and carton labeling received on September 24, 2024 for Imkeldi. We reviewed the IFU and the revised container label and carton labeling for Imkeldi (Appendix A) to determine if they are 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

As currently presented, the established name of Imkeldi, is presented as imatinib (b) (4) however, this does not correlate with the proposed strength of Imkeldi (i.e. the strength is expressed as the active moiety, imatinib). We note that the Office of Pharmaceutical Quality (OPQ) has determined that the established name of Imkeldi should be imatinib, and they will provide a recommendation to revise the labels and labeling accordingly. We find this incongruity between the established name and strength is confusing, which may contribute to medication errors, and we agree with this change from a medication error perspective.

We find that the submitted Instructions for Use (IFU), revised container label and carton labeling are unacceptable from a medication error perspective. We provide our recommendations below.

3 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Instructions for Use (IFU)

- a. Figure A does not have all of the oral syringe components labeled used for the preparation of the proposed product. Lack of adequate labeling of the images may lead to product preparation medication errors. We recommend revising Figure A to ensure that you label the tip of the oral syringe.
- b. As currently presented, Step 3 contains information that should be separated into multiple steps to improve comprehension, and some information contained within this step is not supported within the Prescribing Information (PI).
 - i. Revise Step 3 to “Check the expiration date on the bottle. Do not use if the expiration date has passed. Contact your healthcare provider or pharmacist”.
 - ii. We note that Step 3 advises users to (b) (4). Presenting information that is not supported within the PI may lead to confusion on the proper preparation technique. We recommend removal of the written instruction (b) (4) and the corresponding Figure C. Start Step 4 with the written instruction “Remove the child-resistant bottle cap...”.

^a Kundreskas, J. Label and Labeling Review for Imkeldi (NDA 219097). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 28. TTT ID: 2024-8113.

- c. As currently presented, the preparation step “Push the plunger of the oral syringe all the way up towards the tip to remove (b) (4) air (b) (4) (Figure (b) (4))” is performed after opening the bottle of Imkeldi, but prior to placing the opened bottle on a flat surface. This step may be difficult for the user to perform with an open bottle of Imkeldi in their hand. We recommend reordering this step so that it is performed after opening the bottle of Imkeldi and placing it on a flat surface. Revise to:
- Place the IMKELDI bottle on a flat surface.
 - Check your prescription to find out the number of mL you are supposed to take. Find the number line on the oral dispensing syringe barrel that matches your dose.
 - Push the plunger of the oral dispensing syringe all the way up towards the tip of the oral dispensing syringe to remove air.
 - While keeping the bottle in an upright position, insert the tip of the oral dispensing syringe into the opening of the bottle adapter and push down gently.
- d. As currently presented, Figure K contains an image that is not consistent the written instructions. The written instruction states to turn the bottle upside down, but the image shows the bottle (b) (4). Inaccurate images in the IFU may lead to product preparation errors. We recommend revising Figure K to match the written instructions.

4 RECOMMENDATIONS FOR SHORLA PHARMA LTD

A. General Comments (Container Label and Carton Labeling)

1. There is an inconsistency between the Prescribing Information (PI) and the container label and carton labeling. The “How Supplied” section of the PI states that Imkeldi is packaged as (b) (4) mL bottles whereas the label states the bottle contains 140 mL. Revise the labeling to reflect the actual bottle configuration and ensure the PI, carton labeling, and container label align.

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/s/

JODY K KUNDRESKAS
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NICOLE F IVERSON
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**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: October 2, 2024

To: Matthew Sherdel
Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Samia Alam, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): IMKELDI (imatinib (b) (4))

Dosage Form and Route: oral solution

Application Type/Number: NDA 219097

Applicant: Shorla Pharma Ltd

1 INTRODUCTION

2 On January 31, 2024, Shorla Pharma Ltd submitted for the Agency's review New Drug Application (NDA) 219097 for IMKELDI (imatinib (b) (4)). This original NDA is a kinase inhibitor proposing indications for the treatment of:

- newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
- patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase
- adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia
- adult patients with myelodysplastic/myeloproliferative diseases

This NDA is a 505(b)(2) which references NDA 021588 Gleevec as the listed drug.

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 Hematologic Malignancies I (DHM1) on March 15, 2024 and September 26, 2024, for DMPP and on February 7, 2024, for OPDP to review the Applicant's proposed Instructions for Use (IFU) for IMKELDI (imatinib (b) (4)) oral solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

3 MATERIAL REVIEWED

- Draft IMKELDI (imatinib (b) (4)) IFU received on January 31, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 27, 2024.
- Draft IMKELDI (imatinib (b) (4)) Prescribing Information (PI) received on January 31, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 27, 2024.

4 REVIEW METHODS

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 IFU 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 APFont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

5 CONCLUSIONS

The IFU is acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU 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 IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN

10/02/2024 07:00:08 AM

DMPP-OPDP review of imatinib (b) (4) (IMKELDI) NDA 219097 IFU

SAMIA ALAM

10/02/2024 11:41:03 AM

LASHAWN M GRIFFITHS

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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)

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Date of This Review:	August 28, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219097
Product Name, Dosage Form, and Strength:	Imkeldi (imatinib (b) (4)) Oral Solution, 80 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Shorla Pharma Ltd
FDA Received Date:	January 31, 2024
TTT ID #:	2024-8113
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Imkeldi (imatinib (b) (4) Oral Solution, we reviewed the proposed Imkeldi Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Imkeldi (imatinib (b) (4) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Gleevec (imatinib mesylate) tablets, NDA 021588.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219097.

Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), container labels, and carton labeling for Imkeldi to identify deficiencies that may lead to medication errors and areas of improvement.

The Applicant indicated in their submission that they are pursuing a new presentation of imatinib as an oral solution to simplify the administration to patients who, due to illness or age, are not able to swallow tablets, or who may prefer a liquid formulation.

Imkeldi (imatinib (b) (4) Oral Solution is proposed with the same indications, recommended dosage, and route of administration as the LD, Gleevec (imatinib mesylate) tablets. Imkeldi differs from Gleevec in dosage form (oral solution vs. tablets) and strength (80 mg/mL vs. 100 mg and 400 mg).

We note that the proposed product will not be co-packaged with an oral dosing device and that the Prescribing Information (PI) states that the dispensing pharmacist should provide an appropriate dosing device and measuring instructions. We considered whether commonly available oral dosing syringes would be appropriate to accurately measure all recommended doses of Imkeldi. For example, a 100 mg dose would equal a volume of 1.25 mL and a 600 mg dose would equal a volume of 3.75 mL, volumes which may be difficult to accurately measure to two decimal places. The 100 mg dose would be measured between the 1.2 mL and 1.3 mL graduation marks on the oral syringe, corresponding to a dose range of 96 mg to 104 mg and the 300 mg dose would be measured between the 3.6 mL and 3.8 mL graduation marks, corresponding to a dose range of 288 mg to 304 mg. We informed the Clinical review team of these concerns and requested their input as to the clinical consequence(s) of inadvertent dose rounding due to measuring volumes utilizing commonly available oral dosing syringes. The Clinical review team shared our concerns and requested the Clinical Pharmacology review team

opine. The Clinical Pharmacology review team stated that imatinib is not known to have a narrow therapeutic index and so changes up to 5% due to rounding or measurement inaccuracies should not significantly impact the safety and efficacy. Additionally, as the LD has a pediatric indication and is only available in tablets, rounding to the nearest dose strength occurs in this population and the proposed oral solution would allow more precise dosing than the tablet LD. Lastly, we note that imatinib is an antineoplastic agent which requires special handling and the Office of Pharmaceutical Quality (OPQ) has confirmed that the In Use Stability Study Report^a submitted with the application states “it is recommended that a bottle of Imatinib 80 mg/mL Oral Solution is fitted with a bottle adapter prior to first use to facilitate dose withdrawal with a syringe.”. As such, after further discussion and agreement with the Clinical review team, we provide a recommendation to the Division to request for the Applicant to draft an Instructions for Use (IFU) to ensure that patients and caregivers understand how to use the medication safely and effectively.

We also requested that OPQ provide additional information on the stability of the drug product after removal from the original container, such as after dispensing, and on the stability of the drug product remaining in the original container after opening. OPQ stated that the Applicant did not provide any data to support transferring the drug product to another container, such as for dispensing, and that the drug product should be used within 30 days following opening. As such, we provide recommendations regarding this information. Lastly, we noted that the labeling uses the established name imatinib (b) (4) but the strength expression is stated as imatinib (e.g., each mL contains 80 mg of imatinib, equivalent to 95.57 mg of imatinib mesylate) and we requested OPQ review this information. OPQ stated that the established name and strength matches the presentation of the LD, Gleevec, and no changes are necessary.

The Division of Hematologic Malignancies 1 (DHM 1) requested the review team explore whether dose rounding information should be presented in the PI. We note that the LD does not provide guidance in the PI on dose rounding using tablets. The Clinical and Clinical Pharmacology review teams stated that the proposed oral solution would allow users to measure more precise doses than the LD (100 mg and 400 mg tablets), that imatinib does not have a narrow therapeutic index, and that doses of +/- (b) (4) mg should not impact the safety and efficacy of the product. Because the proposed oral solution is not supplied with a measuring device, dispensing pharmacies must supply an appropriate measuring device with each prescription. As such, we are unable to provide specific, universal recommendations for dose rounding that would encompass all measuring devices that could be supplied by pharmacies. Lastly, we note that the *Patient Counseling* section in the PI instructs pharmacists to provide patients and caregivers instructions for measuring the correct dose. Therefore, the general statement, “Round each dose to the nearest measurable graduation mark on the oral syringe, if necessary [see *Instructions for Use*].” will be included in the PI.

^a In Use Stability Study Report for Imatinib 80 mg/mL Oral Solution NDA 219097. Tipperary (Ireland): Shorla Pharma Ltd; 2024 JAN 31. Available from: <\\CDSESUB1\EVSPROD\nda219097\0001\m3\32-body-data\32p-drug-prod\imat\32p8-stab\stability-data-lmml-stru-17-049-01.pdf>.

4 CONCLUSION

The proposed Imkeldi Prescribing Information (PI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 1 (DHM 1) in Section 5 and for Shorla Pharma Ltd in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. Highlights of Prescribing Information

a. Dosage Forms and Strengths

- i. As currently presented, the strength is presented as "(80 mg/mL): (b) (4)". Drug products not in unit-dose packaging shall be labeled to show the quantity of each active moiety and/or drug substance in each milliliter in accordance with General Chapter <7>. Revise the strength to "80 mg/mL" in accordance with USP General Chapter <7>.

2. Full Prescribing Information

a. Section 2 Dosage and Administration

- i. Imkeldi is a hazardous drug, however, the Dosage and Administration section does not convey this information. Hazardous drugs require special handling procedures. We recommend adding the statement "Imkeldi is a hazardous drug. Follow applicable special handling and disposal procedures.". Include a numerical citation to "OSHA Hazardous Drugs" in the reference section.
- ii. Instructions regarding dose rounding is not present in the Dosage and Administration Section. Lack of instructions on appropriate dose rounding may result in confusion during product preparation. We recommend adding the statement, "Round each dose to the nearest measurable graduation mark on the oral syringe, if necessary." to Section 2.1, Important Administration Instructions.

b. Section 3 Dosage Forms and Strengths

- i. As currently presented, the strength is presented as "(80 mg/ mL): (b) (4)". Drug products not in unit-dose packaging shall be labeled to show the quantity of each active moiety and/or drug substance in each milliliter in accordance with General Chapter <7>. Revise the strength to "80 mg/mL" in accordance with USP General Chapter <7>.

c. Section 16 How Supplied/Storage and Handling

- i. A description of the dosage form is not provided (e.g., a clear yellow to brownish yellow colored solution). A description of

identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(17)(iii). Provide a description of identifying characteristics of the oral solution in accordance with 21 CFR 201.57(c)(17)(iii).

- ii. Imkeldi is a hazardous drug, however, the Storage and Handling section does not convey this information. Hazardous drugs require special handling procedures. We recommend adding the statement "Imkeldi is a hazardous drug. Follow applicable special handling and disposal procedures.". Include a numerical citation to "OSHA Hazardous Drugs" in the reference section.
- iii. Important storage and handling information is missing from this section. Clear handling instructions minimize the risk of deteriorated drug medication errors. We recommend adding "Store and dispense in original container only. Use within 30 days of first opening the bottle, then discard any remainder." to this section.

6 RECOMMENDATIONS FOR SHORLA PHARMA LTD

A. General Comments (Container Label & Carton Labeling)

1. The placement of the graphic at the beginning of the proprietary name competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name. Placing a logo immediately before, within, or after the proprietary name can lead to misinterpretation because logos may look like an additional letter in the proprietary name or detract from legibility. Delete, move, and/or decrease the prominence of the graphic at the beginning of the proprietary name.
2. As currently presented, the strength is presented as " (b) (4) (80 mg/mL)". Drug products not in unit-dose packaging shall be labeled to show the quantity of each active moiety and/or drug substance in each milliliter in accordance with General Chapter <7>. Revise the strength to "80 mg/mL" in accordance with USP General Chapter <7>.
3. The statement (b) (4) uses outdated labeling terminology. We recommend revising this statement to align with current labeling terminology. We recommend revising the statement to "WARNING: Hazardous Drug" in bold font on the principal display panel (PDP) of the container label and carton labeling, or on the side panel if space is limited.
4. The "Rx only" statement appears more prominent than other critical information (e.g., established name) on the Principal Display Panel (PDP). The "Rx only" statement should not compete in size and prominence with critical information on the PDP. We recommend debolding the "Rx only" statement so that it does not compete in size or prominence with critical information on the PDP. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

5. As currently presented, the information to discard the product 30 days after opening is missing and there is no space for end-users to write the beyond-use date which is the date the opened product must be discarded. Since the product has a different expiration date after opening, the container label should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors. We recommend including space for end-users to write the beyond-use date on the container label. For example:

Discard unused portion 30 days after first opening.

(b) (4) ___/___/___

B. Container Label

1. 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).
2. The linear barcode is oriented in a horizontal position on the container. Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode. We recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode.
3. As currently presented, the established name is presented in pink font that lacks legibility on the principal display panel. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend ensuring legibility of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

C. Carton Labeling

1. The product identifier is missing. 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 into 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 place holder to the carton labeling.
2. As currently presented, MM/YYYY, the expiration date format does not follow recently revised USP General Chapter <7> formatting guidelines. USP <7> requires the year, in YYYY format, to be listed at the beginning of the expiration date. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. To minimize confusion and reduce the risk for deteriorated drug medication errors, revise the expiration date format to comply with USP <7> formatting guidelines.
3. The statement (b) (4) should be revised to discourage transfer or repackaging of the drug product to a new container as OPQ has confirmed there is no stability data to support this action. Clear handling instructions minimize the risk of deteriorated drug medication errors. We recommend revising this statement to "Store and dispense in original container only." to be consistent with the Prescribing Information.
4. As currently presented, the established name lacks prominence on the Principal Display Panel (PDP) due to the similarity between the pink boxing color surrounding the statement (b) (4) and the pink font color used for the established name. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend increasing the prominence of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Imkeldi received on January 31, 2024 from Shorla Pharma Ltd, and the Listed Drug (LD).

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).		
Product Name	Imkeldi	Gleevec ^b
Initial Approval Date	N/A	April 18, 2003
Active Ingredient	imatinib mesylate	

^b Gleevec [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. August 2022. [cited 2024 MAR 08]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021588s062lbl.pdf.

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).		
Product Name	Imkeldi	Gleevec ^b
Indication	• Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML) Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. • Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. • Adult Patients With Ph+ Acute Lymphoblastic Leukemia (ALL) Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). • Pediatric Patients With Ph+ Acute Lymphoblastic Leukemia (ALL) Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy. • Myelodysplastic/Myeloproliferative Diseases (MDS/MPD) Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. • Aggressive Systemic Mastocytosis (ASM) Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown. • Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL) Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown. • Dermatofibrosarcoma Protuberans (DFSP) Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans. • Kit+ Gastrointestinal Stromal Tumors (GIST) Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. • Adjuvant Treatment of GIST	

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).		
Product Name	Imkeldi	Gleevec ^b
	Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.	
Dosage Form	Oral Solution	Tablets
Strength	80 mg/mL	100 mg and 400 mg
Route of Administration	Oral	

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).

Product Name	Imkeldi	Gleevec ^b
Dose and Frequency	• Adult Patients With Ph+ CML CP, AP, or BC 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6 to 12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response. • Pediatric Patients With Ph+ CML CP 340 mg/m²/day (not to exceed 600 mg). Treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with treatment in children under 1 year of age. • Adult Patients With Ph+ ALL 600 mg/day for adult patients with relapsed/refractory Ph+ ALL. • Pediatric Patients With Ph+ ALL	• Adult Patients With Ph+ CML CP, AP, or BC 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6 to 12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response. • Pediatric Patients With Ph+ CML CP 340 mg/m²/day (not to exceed 600 mg). Treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with treatment in children under 1 year of age. • Adult Patients With Ph+ ALL 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).

Product Name	Imkeldi	Gleevec ^b
	To be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m²/day (not to exceed 600 mg). Treatment can be given as a once daily dose. • Adult Patients With MDS/MPD 400 mg/day for adult patients with MDS/MPD. • Adult Patients With ASM 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c- Kit mutational status is not known or unavailable, 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. • Adult Patients With HES/CEL 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. • Adult Patients With DFSP 800 mg/day for adult patients with DFSP.	• Pediatric Patients With Ph+ ALL To be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m²/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose. • Adult Patients With MDS/MPD 400 mg/day for adult patients with MDS/MPD. • Adult Patients With ASM 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. • Adult Patients With HES/CEL 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).

Product Name	Imkeldi	Gleevec ^b
	• Adult Patients With Metastatic and/or Unresectable GIST 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions. • Adult Patients With Adjuvant GIST 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In clinical trials, one year of Imkeldi and three years of Imkeldi were studied. In the patient population defined in Study 2, three years of Imkeldi is recommended. The optimal treatment duration with Imkeldi is not known.	from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. • Adult Patients With DFSP 800 mg/day for adult patients with DFSP. • Adult Patients With Metastatic and/or Unresectable GIST 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions. • Adult Patients With Adjuvant GIST 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In clinical trials, one year of Gleevec and three years of Gleevec were studied. In the patient population defined in Study 2, three years of Gleevec is recommended. The optimal treatment duration with Gleevec is not known.

Table 2. Relevant Product Information for Imkeldi and the Listed Drug (LD).		
Product Name	Imkeldi	Gleevec ^b
How Supplied	Imkeldi 80 mg/ml Oral Solution is packaged in (b) (4) ml Amber PET bottle with a child resistant tamper-evident closure. NDC 81927-201-01	Each film-coated tablet contains 100 mg or 400 mg of imatinib free base. 100-mg tablets Very dark yellow to brownish orange, film-coated tablets, round, biconvex with bevelled edges, debossed with "NVR" on one side, and "SA" with score on the other side. Bottles of 90 tablets: NDC 0078-0401-34 400-mg tablets Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with "gleevec" on one side and score on the other side. Unit Dose (blister pack of 30): NDC 0078-0649-30
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight container, USP.
Container Closure	Imatinib Oral Solution (80mg/mL) is provided in a (b) (4) mL amber polyethylene terephthalate (PET) bottle with a 28 mm (b) (4) Child Resistant Cap with (b) (4) liner. The (b) (4)	100 mg tablets: (b) (4) (b) (4) bottles of 90 (b) (4) 400 mg tablets: Carton containing one blister pack of 30 tablets

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Imkeldi labels and labeling submitted by Shorla Pharma Ltd.

- Prescribing Information received on January 31, 2024, available from <\\CDSESUB1\EVSPROD\nda219097\0001\m1\us\1-14-1-3-drft-label-txt.pdf>
- Container label(s) received on January 31, 2024
- Carton labeling received on January 31, 2024

B.2 Container Label and Carton Labeling Images

Container Label:



Carton Labeling:

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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