Clinical and Labeling Review

Product Title and Strength	Imkeldi (imatinib) oral solution; 80 mg/mL
Applicant	Shorla Pharma LTD
Application/Supplement Number	NDA 219097
Type of Application/Submission	505(b)(2) NDA
Proposed Indications	• 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 (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy. • Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). • Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy. • Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown. • Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) 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. • Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP). • Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). • Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.
Date of Submission	January 31, 2024
Review Classification (Priority/Standard)	Standard
PDUFA Goal Date	November 30, 2024
Recommendation on Regulatory Action	Regular Approval
Review Date	October 10, 2024
Clinical Reviewer	Yanxia Li, MSN, CRNP
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP
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Background and Summary:

Imatinib oral solution, 80 mg/mL (400 mg/5 mL) is being developed as an alternative dosage form for the ease of administration to patients who, due to illness or age, are not able to swallow tablets, or who may prefer a liquid formulation.

The Applicant is seeking the following indications (the same as the listed drug):

- 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 (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy.
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) 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.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.

The listed drug, Gleevec imatinib mesylate tablets are available in 100 mg and 400 mg strengths. Imatinib was initially approved as Gleevec capsules in May 2001 and as Gleevec tablets in April 2023 in the United States (imatinib mesylate tablet; Novartis Pharmaceuticals Corp, NDA 021588).

Regulatory History:

Shorla Pharma Ltd. submitted this New Drug Application (NDA) via the 505(b)(2) regulatory pathway for Imatinib Oral Solution, 400 mg/5 mL (80 mg/mL), as an alternative dosage form for the ease of administration to patients who, due to illness or age, are not able to swallow tablets, or who may prefer a liquid formulation.

A Type B PIND meeting for Imatinib Oral Solution was held on March 5, 2018.

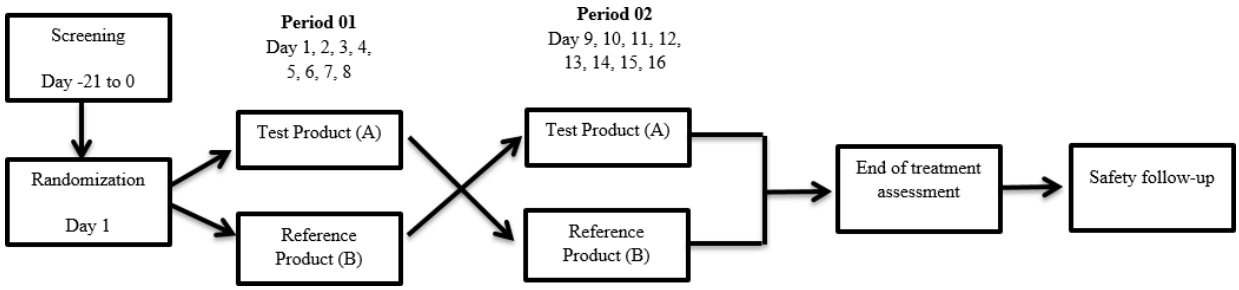
An initial iPSP agreement letter was issued on June 30, 2021, for pediatric patients (1- <17 years old) with chronic phase Ph+ CML and Ph+ ALL.

Clinical Review:

The applicant conducted 1 pivotal bioequivalence study in patients on a stable dose of imatinib which is summarized below. The reference product is a tablet formulation, and the proposed product is an oral solution, hence a pivotal bioequivalence study was conducted comparing the test and reference products. See clinical pharmacology review for details on establishing bioequivalence to imatinib with similar exposure to corresponding strengths of Gleevec. This review focuses on clinical safety.

Pivotal Study: Clinical Study CBCC/2018/013:

Study design flow chart



- Treatment A= Test Product (Imatinib Mesylate) Oral Solution 400mg/5ml; Manufactured by: (b) (4) (b) (4) Manufactured for (b) (4)
- Treatment B= Reference Product [Gleevec (Imatinib mesylate)] Tablets 400mg of Distributed by Novartis Pharmaceuticals Corporation
- End of treatment assessment was performed on Day 17 or at the time of early discontinuation
- Safety follow up was performed 7 (±3) days after the completion of treatment period

This is 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 (b) (4) with Gleevec (Imatinib mesylate) Tablets 400 mg, in adult human patients with chronic myeloid leukemia and/ or gastrointestinal stromal tumors under fed condition conducted at multiple study centers in India.

- Primary objective: To compare and evaluate the multiple-dose oral bioavailability of Imatinib Mesylate Oral Solution 400 mg/5 mL with Gleevec (imatinib mesylate) Tablets 400 mg in adult human patients with CML and/or GIST under fed condition.
- Secondary Objective: To monitor the adverse events and to ensure the safety of patients.
- Study population:
    - Chronic Myeloid Leukemia or Gastrointestinal Stromal Tumors
    - On a stable dose of 400 mg Imatinib monotherapy

    - Age 18 to 65 years (both inclusive)
    - Body Mass Index (BMI) at least 17.00 kg/m2.
- 46 patients were screened; 35 patients were enrolled. Patients that withdrew or discontinued from the study were not replaced. Total of 32 patients completed the study.
- As per the randomization schedule, the investigational products were administered once daily to each patient from Day 01 to 08 (Period 01) and Day 09 to 16 (Period 02).
- Total study duration was approximately 45 days consisting of: Screening Period: up to 21 days, Treatment Period: 17 days, from day 01 in Period 01 till last PK blood sample collection in period 02, i.e., on Day 17 of the study and safety follow-up visit 7 ± 3 days after completion of treatment period.
- Safety Results:
    - A total of 8 TEAEs were reported in 6/35 (17.1%) patients over the course of the study. No SAE or death reported during the study.
    - Out of 8 TEAEs, 2 AEs were mild, and 6 AEs were moderate in intensity.
    - Out of 8 TEAEs, 1 AE was probably related, 6 AEs were possibly related, and 1 AE was unrelated to study drug by the investigator's assessment.
    - Out of 8 TEAEs, 3 AEs were reported in 2/17 (11.8%) patients in the group AB (imatinib-Gleevec) and 5 AEs were reported in 4/18 (22.2%) patients in group BA (Gleevec-imatinib).
    - TEAEs following administration of test product (imatinib solution): 3 TEAEs occurred in two patients for constipation, neutropenia, and white blood cell count decreased.
    - TEAEs following administration of reference product (Gleevec): 5 TEAEs occurred in four patients for diarrhea, Covid-19, pain in extremity, dizziness, and platelet count decreased.
    - One patient withdrew from the study due to an AE of Covid-19 infection - Subject # (b) (6) from treatment sequence BA, period 1, treatment B (Gleevec). Two patients withdrew from the study due to due to Protocol Specified Withdrawal / Discontinuation Criteria met - Subject (b) (6) and subject (b) (6) both from sequence BA, treatment period 1 (Gleevec), no specified withdrawal /discontinuation criterion provided

Clinical reviewer assessment: Both medicinal products contain the same active substance (imatinib mesylate). The adverse events observed in this trial are comparable to the known safety profile of Gleevec. Two patients receiving experienced three adverse events after receiving imatinib solution, and these events have been reported with Gleevec and were mild to moderate.

The test product has some dose difficult to accurately administer with 80 mg/mL solution, e.g., 100 mg starting dose requires 1.25 ml, there are detailed recommendations from the labeling review as below.

Overall, there are no safety concerns that preclude approval for this product from the clinical perspective.

Pediatrics:

The investigational product is a new dosage form of imatinib and therefore is subject to PREA requirements for pediatric investigations. The applicant submitted an assessment for pediatric patients 1 year of age and older with newly diagnosed Ph+ CML in chronic phase and Ph+ ALL and a request for partial waiver for studies in pediatric patients less than 1 year of age for those indications. Section 8.4 of Gleevec states that there are no data in children under one year of age, though the indications for CML and ALL are not limited by age. The applicant is also requesting a full waiver for all

other indications sought. This was consistent with the agreed iPSP that was submitted and agreed on 6/30/2021.

Labeling Review:

The following substantive changes made by the FDA to the USPI are described below; for final agreed upon labeling, see the approval letter for NDA 219097:

- In the Highlights, the product title was corrected, and the Warning and Precaution titles for the summary statements and missing cross-references were added.
- In section 2 Dosage and Administration:
  - The title for subsection 2.1 was changed to "Important Administration Instructions". Instructions about missed dosages, recommendations for dose rounding, and a cross-reference to the instructions for use (IFU) were added. An IFU was determined to be necessary for safe use by FDA due to concerns with accurate measurement of the oral solution, given the need to use an adaptor to assure an accurate dosage. See the reviews of the applicant's proposed IFU by the Division of Medical Error Prevention and Analysis and the Division of Medical Policy Programs filed separately in DARRTS.
  - In subsections 2.3 and 2.4 dosage in pediatric patients, instructions were added to follow dose rounding recommendations in subsection 2.1.
  - In subsection 2.12 dosage modifications for drug interactions, hepatic impairment, and renal impairment, information was reordered and statements about specific numbers of patients tolerating concomitant use of CYP3A4 inducers with imatinib and patients with severe renal impairment tolerating a dose of 100 mg/day included in the listed drug's labeling were removed as these statements do not align with current recommendations in guidance for inclusion in the USPI.
- Drug Interactions subsections 7.1, 7.2, 7.3, and 7.4 were updated to align with current labeling recommendations, including actions to be taken when Imkeldi is used with specific agents as well as how exposure of imatinib or a substrate is affected when used concurrently.
- Use in Specific Populations subsections 8.6 and 8.7 for renal and hepatic impairment were modified to include actionable recommendations for dosage adjustments. (b) (4) (b) (4) were removed as they do not align with labeling recommendations.
- Clinical Pharmacology section 12:
  - A new subsection 12.2 Pharmacodynamics added to note that imatinib exposure-response relationships and the time course of pharmacodynamic response are unknown. This aligns with 21 CFR 201.57(c)(13)(i)(B) which states that this information must be included if known, or if unknown, the lack of that information must be included.
  - In subsection 12.3 Pharmacokinetics, changes were made to align with recommendations in guidance, and dosage qualification statements stating "x times the recommended dosage" added to qualify reference to unapproved dosages to align with 21 CFR 201.57(c)(3)(ii) which states that dosages must not be implied or suggested in other sections of the label if not included in section 2 Dosage and Administration.
- Clinical Studies section 14:

- Throughout this section, any reference to unapproved dosages were qualified as being "x times the recommended dosage" to align with 21 CFR 201.57(c)(3)(ii) which states that dosages must not be implied or suggested in other sections of the label if not included in section 2 Dosage and Administration.

Recommended Regulatory Action:

Considering safety and if bioequivalence is established, the clinical review team recommends regular approval of imatinib oral solution, 80 mg/mL by Shorla Pharma for the following indications:

- 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 (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy.
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
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- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.

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