CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219097Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader and Division Director Review

Date	See stamp date
From	Lori Ehrlich, MD, PhD; Cross-Discipline Team Leader Kelly Norsworthy, MD; Deputy Division Director
Subject	Cross-Discipline Team Leader and Division Director Review
NDA/BLA # and Supplement#	NDA 219097
Applicant	Shorla Pharma Ltd
Date of Submission	January 31, 2024
PDUFA Goal Date	November 30, 2024
Proprietary Name	Imkeldi
Established or Proper Name	Imatinib oral solution
Dosage Form(s)	Oral solution: 80 mg/mL
Applicant Proposed Indication(s)/Population(s)	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 (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.
Applicant Proposed Dosing Regimen(s)	• Adults with Ph+ CML CP: 400 mg/day • Adults with Ph+ CML AP or BC: 600 mg/day • Pediatrics with Ph+ CML CP: 340 mg/m^2/day • Adults with Ph+ ALL: 600 mg/day • Pediatrics with Ph+ ALL: 340 mg/m^2/day • Adults with MDS/MPD: 400 mg/day • Adults with ASM: 100 mg/day or 400 mg/day • Adults with HES/CEL: 100 mg/day or 400 mg/day • Adults with DFSP: 800 mg/day • Adults with metastatic and/or unresectable GIST: 400 mg/day • Adjuvant treatment of adults with GIST: 400 mg/day • Patients with mild to moderate hepatic impairment: 400 mg/day • Patients with severe hepatic impairment: 300 mg/day
Recommendation on Regulatory Action	*Regular Approval*
Recommended Indication(s)/Population(s)	As proposed by Applicant
Recommended Dosing Regimen(s)	As proposed by Applicant

Material Reviewed/Consulted	Reviewer
Clinical Review	Yanxia Li, MSN, CRNP / Lori Ehrlich, MD, PhD
Labeling Review	Elizabeth Everhart, MSN, RN, ACNP
Nonclinical Review	Monica Feng, PhD / Brenda Gehrke, PhD
Clinical Pharmacology Review	Mathew John, PhD; Nan Zheng, PhD
CMC Review	DS: Siva Mandadapu, PhD / Haripada Sarker, PhD DP: Damien Duveau, PhD / Olen Stephens, PhD Manufacturing: Steve Hertz, PhD / James Norman, PhD

1. Regulatory Action

Recommended Regulatory Action: Regular Approval

The bioequivalence of imatinib oral solution (Imkeldi) to imatinib tablets (Gleevec, reference product) was investigated in one pivotal bioequivalence study:

- Clinical Study CBCC/2018/013: 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 400mg/5ml of (b) (4) (b) (4) with Gleevec® (Imatinib mesylate) Tablets 400mg 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.

The recommended dosing is 300-800 mg/day for adult patients dependent on the disease and organ impairment and 340 mg/m^2/day in pediatric patients.

From a clinical pharmacology perspective, the Applicant provided data to support that 400 mg of Imkeldi is bioequivalent to 400 mg of Gleevec. Pharmacology/toxicology review team also concluded that Imkeldi was approvable. Clinical noted that no new safety signals were identified with adverse events observed consistent with the known safety profile of the listed drug, and the application was approvable from a clinical perspective. The CMC review team determined that the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective.

Approach to Substantial Evidence of Effectiveness

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:
   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 (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.

2. Proposed approval pathway
   a. ☒ Traditional
   b. ☐ Accelerated approval (21 CFR 314.500, Subpart H; 21 CFR 601.40, Subpart E)
   c. ☐ Animal rule (21 CFR 314.600, Subpart I; 21 CFR 601.90, Subpart H) *(if checked, omit item 5)*
3. Action
   a. ☒ Approval
   b. ☐ Tentative approval
   c. Complete response (check all that apply)
      i. ☐ SEE was not established *(if checked, omit item 5)*
      ii. ☐ Product quality issues
      iii. ☐ Safety concerns (benefit/risk)
      iv. ☐ Other: Click here to enter other reason(s) for complete response.
5. SEE was established with *(check one of the options for traditional or accelerated approval pathways)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ At least two adequate and well-controlled clinical investigations, OR
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations
      Description optional.

      OR
   b. ☐ One adequate and well-controlled clinical investigation supported by confirmatory evidence[1,2,3]

      Description optional.

      OR
   c. ☒ Evidence that supported SEE from a prior approval of the drug and was determined, through extrapolation, to provide SEE for the new use/indication *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; pediatric extrapolation; extrapolation of data from immediate-release dosage form to new extended-release dosage form; over-the-counter switch)*[2]

      505(b)(2) application for imatinib oral solution (Imkeldi) that relied on the determination of effectiveness from the reference drug, Gleevec.

[1] FDA draft guidance for industry Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019)
[2] FDA guidance for industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (1998)

[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

2. Background

On January 31, 2024, Shorla Pharma Ltd (Applicant) submitted a 505(b)(2) New Drug Application (NDA 219097) for imatinib oral solution (Imkeldi), with a proposed dosage of is 300-800 mg/day for adult patients dependent on the disease and organ impairment and 340 mg/m^2/day in pediatric patients. Imkeldi is to be provided as oral solution, 80 mg/ml (400 mg per 5 mL). The Applicant proposed the 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 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 associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- 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.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.
- Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

Gleevec (imatinib mesylate) is the listed drug upon which the 505(b)(2) application relied. Initial U.S. approval for Gleevec was in 2001 as Gleevec capsules and in 2003 as Gleevec tablets. The Applicant is seeking the same indications and dosages as currently approved for Gleevec, which are listed above. Gleevec is available as 100 mg and 400 mg tablets.

Imatinib oral solution (Imkeldi), 80 mg/mL, is being developed as an alternative dosage form for 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.

3. Product Quality

From the Executive Summary of the CMC Review and the discipline-specific summaries, the following excerpts are noted:

> OPQ recommends APPROVAL of NDA 219097 for the commercialization of IMKELDI (imatinib) oral solution. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.
>
> Drug Substance:
> The drug substance CMC information for imatinib mesylate is cross referenced to DMF (b) (4) DMF (b) (4) was reviewed (R4_AQ) by Sivakoteswara rao Mandadapu on 12-September-2024 (Panorama) in support of this NDA and found adequate. The applicant provides a brief description of the general properties of the drug substance, impurities, and drug substance specification. The applicant provided details on the tests performed upon acceptance of drug substance from the supplier ((b) (4) (b) (4), and method verification data are provided. The NDA is recommended for approval from the perspective of drug substance quality.
>
> Drug Product:
> Assessment Recommendation: Adequate
>
> Manufacturing:
> Facility Assessment Recommendation: Adequate
> Process Assessment Recommendation: Adequate
> The drug product (Imatinib Oral Solution, 80 mg/ml) is provided as a clear yellow to brownish yellow colored solution (b) (4) in an amber color PET (polyethylene terephthalate) bottle, indicated for newly diagnosed adult and pediatric patients with Philadelphia chronic phase. The proposed commercial manufacturing process consists (b) (4) (b) (4) Process deficiencies were identified and communicated to the Applicant via information requests. The Applicant responded adequately to these identified process deficiencies. All proposed commercial manufacturing facilities were deemed adequate to perform the responsibilities as listed in the application.
>
> Microbiology:
> Assessment Recommendation: Adequate

Assessment Summary: This is a multi-dose non-sterile oral drug product. The manufacturing process is to be controlled for [redacted] (b) (4) [redacted] (b) (4) Supporting data meet the quality microbiology review criteria.

4. Nonclinical Pharmacology/Toxicology

From the Summary of the Pharmacology/Toxicology Review,

> Imatinib Oral Solution, 80 mg/mL has been developed as a new presentation form of imatinib as an oral solution to simplify the administration to patients who are not able to swallow tablets due to illness or age or who may prefer a liquid formulation. The active pharmaceutical ingredient (API), route of administration, dosing regimen, and indications sought for the proposed imatinib formulation are the same as the LD, Gleevec. The excipient profile of the proposed imatinib mesylate liquid formulation differs from Gleevec.
>
> The Applicant's imatinib mesylate formation is a [redacted] (b) (4) of Gleevec, and the current application is relying in part upon the Agency's previous findings of safety and efficacy for Gleevec as described in the approved labeling.
>
> Recommended for approval. There are no Pharmacology/Toxicology concerns with the proposed Imatinib Oral Solution drug product.

5. Clinical Pharmacology

From the Executive Summary of the Clinical Pharmacology Review,

> This submission provides comparative bioavailability (BA) data and safety information from a pivotal in vivo bioequivalence (BE) study (MW180013) in patients with CML or GIST who were on a stable dose of 400 mg once daily (QD) imatinib monotherapy in the fed condition. Imatinib oral solution was bioequivalent to the tablet as evident by geometric mean ratio (GMR) (90% confidence interval [CI]) of 102.6% (92.9% – 113.9%) and 102.3% (92.2% – 113.5%) for steady state AUC and Cmax, respectively. The Applicant has submitted the clinical study report and associated datasets to support the claim that the proposed imatinib oral solution is bioequivalent to the LD.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical – Efficacy

No clinical efficacy data were submitted. Imatinib oral solution (Imkeldi) by Shorla Pharma Ltd is another formulation of imatinib mesylate. The Applicant's proposed formulation (oral solution, 400 mg in 5 mL) is bioequivalent with Gleevec (reference product) with similar exposure to Gleevec (400 mg). The Applicant proposed to rely on the established efficacy of Gleevec.

8. Clinical – Safety

Source: Clinical Review

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 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.

9. Advisory Committee Meeting

This product is not a new molecular entity and did not require Advisory Committee discussion.

10. Pediatrics

Source: Clinical Review

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.

The Applicant included a request for the pediatric indications currently approved for the LD.

11. Other Relevant Regulatory Issues

The application was reviewed by the 505(b)(2) clearance committee and was cleared for a Regular Approval action.

Financial disclosure:
Study CBCC/2018/013 established bioequivalence of Imkeldi to the LD to allow extrapolation from the previous determination of effectiveness from the LD. Disclosure of financial interests (form 3455) were provided in Module 5.3.1.2 (SN0001) for 16 investigators at 4 sites. No financial interests were disclosed. Disclosure information was not provided in Module 1.3.4.

12. Labeling

All review teams participated with the labeling review.

The proposed labeling for the Imkeldi is essentially the same in content as that of the innovator listed drug product (Gleevec), except for the following major differences:

- The established name is imatinib (b) (4) consistent with the strength based on the active moiety.
- An instructions for use (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.
- In subsections 2.3 and 2.4 dosage in pediatric patients, instructions were added to follow dose rounding recommendations in subsection 2.1.
- Updates in dosage modifications, drug interactions, and use in specific populations to align with current labeling recommendations.
- In the 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.
- In subsection 12.3 pharmacokinetics and clinical studies section 14, 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.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Not applicable.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Not applicable.

14. Recommended Comments to the Applicant

None.

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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11/21/2024 05:48:18 PM

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