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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number (SDN)	219097
Link to EDR	\\CDSESUB1\evsprod\NDA219097\0001
Submission Date	January 31, 2024
Submission Type	Standard
Brand Name	IMKELDI
Generic Name	Imatinib
Dosage Form and Strengths	Oral Solution, 80 mg / mL
Route of Administration	Oral
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.
Applicant	Shorla Pharma Ltd.
OCP Review Team	Mathew John, Ph D; Nan Zheng, Ph D
OCP Final Signatory	Brian Booth, Ph D

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1. EXECUTIVE SUMMARY

Imatinib is a protein-tyrosine Kinase Inhibitor (TKI) that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). The current submission is a 505(b)(2) New Drug Application for IMKELDI (imatinib oral solution, 80 mg/mL) from Shorla Pharma (Applicant). The listed drug (LD) is GLEEVEC® (Imatinib mesylate tablets, 100 mg and 400 mg) which was approved in April 2003 under NDA 021588. The Applicant is seeking approval for all the approved indications of the LD at the approved dosages.

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.

1.1 Recommendations

The Office of Clinical Pharmacology recommends approval of this NDA. Bioequivalence between the proposed imatinib oral solution, 400 mg/5 mL (80 mg/mL) and 400 mg of GLEEVEC® tablets was demonstrated in the pivotal study.

1.2 Post-Marketing Requirements and Commitment

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Imatinib is an oral Tyrosine Kinase Inhibitor (TKI). The following is a summary of the clinical pharmacokinetics (PK) of imatinib. The following PK parameters are from GLEEVEC® label.

Pharmacokinetics

The pharmacokinetics of imatinib have been evaluated in studies in healthy subjects and in population pharmacokinetic studies. No clinically significant difference in imatinib pharmacokinetics were observed between CML and GIST patients. Imatinib AUC increases proportionally with increasing doses ranging from 25 mg to 1000 mg (0.06 to 1.25 times the approved recommended dosage of 400 mg). Imatinib accumulation is 1.5- to 2.5- fold at steady state when imatinib is dosed once daily.

Absorption

Imatinib mean absolute bioavailability is 98%. Imatinib is well absorbed after oral administration with maximum concentration (C_{max}) achieved within 2-4 hours post-dose.

Distribution:

Imatinib and the N-demethylated metabolite (CGP74588) plasma protein binding is approximately 95% in vitro, mostly to albumin and α1-acid glycoprotein.

Metabolism

Imatinib is primarily metabolized by CYP3A4. CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative (CGP74588), formed predominantly by CYP3A4. It shows in vitro potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

Elimination

The mean elimination half-life is approximately 18 hours for imatinib and 40 hours for the N-demethyl derivative metabolite (CGP74588), following oral administration in healthy volunteers.

Excretion

Imatinib elimination is predominately in the feces, mostly as metabolites. Following an oral radio-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Specific Populations

Hepatic Impairment

Exposure to both imatinib and CGP74588 was comparable between each of the mildly (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1 to 1.5 times ULN) and moderately (total bilirubin > 1.5 to 3 times ULN and any value for AST) hepatically impaired groups and the normal group.

Patients with severe hepatic impairment (Total bilirubin > 3 to 10 times ULN and any value for AST) tend to have higher exposure to both imatinib and CGP74588 than patients with normal hepatic function. At steady state, the mean C_{max}/dose and AUC/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean C_{max}/dose and AUC/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Renal Impairment

The mean exposure to imatinib (AUC/dose) in patients with mild (CLcr = 40-59 mL/min) and moderate (CLcr = 20-39 mL/min) renal impairment increased 1.5- to 2-fold compared to patients with normal renal function. The AUCs did not increase for doses greater than 600 mg in patients with mild renal impairment. The AUCs did not increase for doses greater than 400 mg in patients with moderate renal impairment. Dose reductions are necessary for patients with moderate and severe renal impairment.

Drug Interactions:

- Imatinib is a CYP3A4 substrate and an inhibitor of CYP3A and CYP2D6.
- Imatinib oral-dose clearance increased by 3.8-fold, which significantly (p less than 0.05) decreased mean Cmax and AUC, following pretreatment of healthy volunteers with multiple doses of rifampin (CYP3A inducer) followed by a single dose of imatinib.
- There was a significant increase in imatinib exposure (mean Cmax increased by 26% and mean AUC increased by 40%) in healthy subjects following concomitant use of imatinib with a single dose of ketoconazole (CYP3A4 inhibitor).
- Simvastatin (CYP3A4 substrate) mean Cmax increased 2-fold and AUC 3.5-fold, following

concomitant use with imatinib.

- Metoprolol (CYP2D6 substrate) mean Cmax and AUC increased by approximately 23% following concomitant use with imatinib.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended oral dosage of IMKELDI will follow that for GLEEVEC® for the approved indications, ranging from 400 mg/day to 800 mg/day for adult patients and 340 mg/m^2/day for pediatric patients. The recommendation is based on scientific bridging established in Study MW180013. Study MW180013 demonstrated that the bioavailability of 400 mg / 5 ml imatinib oral solution is comparable to 400 mg of GLEEVEC® tablets, in that the 90% CI of the GMR for primary PK parameters, $C_{max,ss}$ (steady state Cmax) and $AUC_{0-t,ss}$ (steady state AUC during the dosing interval) ,were within bioequivalence limits of 80% to 125% (Table 1).

Table 1: Summary statistics for bioequivalence evaluation (Study MW180013)

Parameter (unit)	IMKELDI oral solution, 400 mg / 5 ml (Test)	GLEEVEC® 1 x 400 mg (Reference)	GMR of Test / Reference (%)	Intra-subject %CV	90% Confidence Interval of GMR
Geometric Mean					
$C_{max,ss}$ (ng/mL)	3676.9	3594.9	102.3	20.9	92.2 – 113.5
$AUC_{0-t,ss}$ (h*ng/mL)	56052.8	54619.8	102.6	20.0	92.9 -113.9

Source: Unscaled average BE results, adapted from Page 75 of study report MW180013

IMKELDI should be taken with food to minimize gastrointestinal (GI) irritation.

2.2.2 Therapeutic individualization

The recommendations on therapeutic individualization will generally follow those for GLEEVEC®. IMKELDI has additional recommendations for accurate measurement in the device (oral syringe) intended for administration of the oral solution as “Round each dose to the nearest measurable graduation mark on the oral syringe”.

2.3 Outstanding Issues

There are no outstanding issues.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Imatinib is a protein tyrosine kinase inhibitor (TKI). GLEEVEC® (imatinib mesylate) tablets was approved in April 2003 for indications including 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 in chronic phase (CP) after failure of interferon-alpha therapy and adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). GLEEVEC® is available as 100 mg and 400 mg strength tablets.

For the treatment of chronic phase Ph+CML, the recommended dose for GLEEVEC® is 400 mg once daily (QD). For treatment of AP or BC Ph+CML, the recommended dose is 600 mg QD. The recommended pediatric dose for chronic phase Ph+CML and Ph+ALL is 340 mg/m^2/day. GLEEVEC® should be taken with food to minimize GI irritation.

In this submission, Shorla Pharma (the Applicant) is seeking approval for IMKELDI oral solution under the 505(b)(2) pathway for all indications of GLEEVEC®. The Applicant has developed IMKELDI 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 claims that the solution dosage form is convenient for physicians or patients who can dose titrate by volume to achieve the precise dose, which can vary from 100 mg-800 mg instead of the necessity for multiple tablet strengths. The clinical pharmacology program included one BE study / assessment in the fed condition:

1) A bioequivalent study (Study MW180013) to support the claim that Test Product (A): Imatinib oral solution 400 mg / 5 ml is bioequivalent to Reference Product (B): 400 mg GLEEVEC® tablets under the fed condition.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Refer to Section 2.1 for the PK parameters.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The clinical pharmacology study provides supportive evidence based on establishment of a scientific bridge (refer to Section 3.3.2) to support the extrapolation of the efficacy and safety of imatinib from GLEEVEC® tablets (NDA 021588).

3.3.2 Has a scientific bridge has been established between drug product(s) used in the literature studies and the proposed drug product to support the acceptance of the scientific literature?

Yes. A scientific bridge has been established between the 400 mg strength of the listed drug (i.e., GLEEVEC®) and the 400 mg / 5 ml strength of IMKELDI oral solution.

The Applicant conducted an open label, multicenter randomized, two-treatment, two-sequence, two-period, two-way crossover multiple dose steady state comparative oral bioavailability study in adult patients with chronic myeloid leukemia and/or gastrointestinal stromal tumor (Table 2).

Table 2: Design of Study MW180013

Purpose	Relative bioavailability of Imatinib mesylate oral solution 400 mg/5mL, test (A) against the approved Gleevac® Tablets, 400 mg reference (B).
Study Design	Randomized, two-treatment, two-sequence, two-period, two-way crossover multiple dose steady state. Subject fasted for 10 hours and consumed non high fat calorie breakfast (300-400 calories).
Study Population	Thirty-five subjects were enrolled into the study. Thirty-two subjects completed the study.
Proposed Dose	Patients received 5 mL (400 mg) of test (A) and one tablet (400 mg) of reference (B) once daily from Day 01 to 08 (Period 01) and Day 09 to 16 (Period 02).
Instruction for Concomitant Medication (DDI Potential)	• Not to consume grapefruit or grapefruit containing products. • Not to consume drugs that are inhibitors and/or inducers of CYP3A4.

PK Sampling Schedule	Day 1, 6, 7, 14, 15: Pre-dose Day 8 and Day 16: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours post dose.
ECG Monitoring Schedule	At screening, day 7, day 15 and end of treatment.

Table 3: Summary of PK Parameters

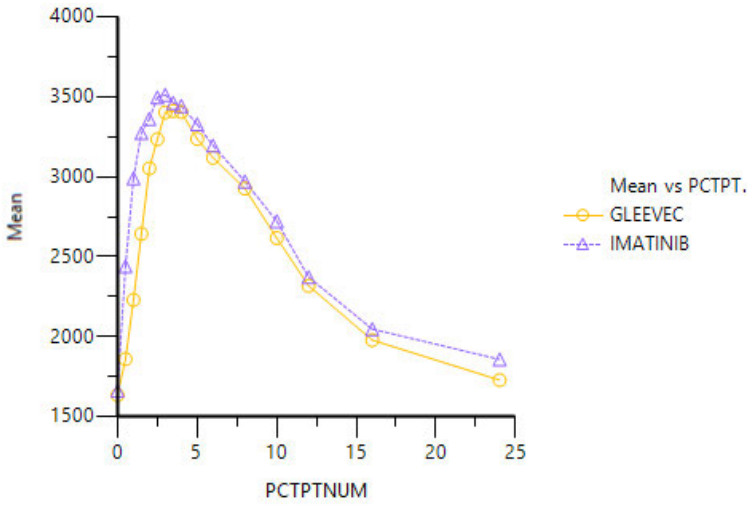
	Arithmetic Mean ± SD, N=32	
Parameter (unit)	IMKELDI oral solution (Test)	GLEEVEC® (Reference)
$C_{max,ss}$ (ng/mL)	3842.7 ± 1415.5	3725.0 ± 1217.2
$AUC_{0\text{-}tss}$ (h*ng/mL)	60575.2 ± 24370.3	57595.3 ± 19083.7
Tmax (hr)*	3.3 (1.0 - 8.0)	4.0 (1.0 - 8.0)

*median (range)

The Applicant conducted the primary analysis using PK data from 24 patients who reached steady state as demonstrated in a pre-specified assessment on trough concentrations. The reviewer was able to reproduce the statistical analysis on bioequivalence evaluation. The reviewer conducted additional sensitivity analyses as described below:

1. BE assessment on the entire datasets (including patients who did not meet the pre-specified criteria for steady state condition). The descriptive statistics of imatinib PK and BE assessment results are presented in Table 4. The 90% confidence intervals of the GMR for $C_{max,ss}$ and $AUC_{0\text{-}t,ss}$ were within the acceptable BE limits of 80% to 125%.

Figure 1: Time-Imatinib concentration profile of the reference product (GLEEVEC®) and the test product (IMKELDI) – entire dataset



Source: Reviewer's analysis

Table 4: Summary statistics for bioequivalence evaluation (entire dataset, N=32)

Parameter (unit)	IMKELDI oral solution, 400 mg / 5 ml (Test)	GLEEVEC® 1 x 400 mg (Reference)	GMR of Test / Reference	90% Confidence Interval of GMR
Geometric Mean				

$C_{max,ss}$ (ng/mL)	3619.4	3535.1	102.4	92.2 – 118.9
$AUC_{0\text{-}tss}$ (h*ng/mL)	56473.5	54766.3	103.1	97.1- 109.4

Source: Reviewer's analysis

2. BE assessment excluding data from clinical site #252. At the time of this review, clinical site inspection for Kailash Cancer Hospital and Research Center (Site ID: 252) has not been cleared due to delays in the travel arrangement. The Reviewer conducted a sensitivity analysis excluding data from this site (Site ID: 252). The results are tabulated below.

Figure 2: Time-Imatinib concentration profile of the reference product (GLEEVEC®) and the test product (IMKELDI) – Excluding Site ID 252

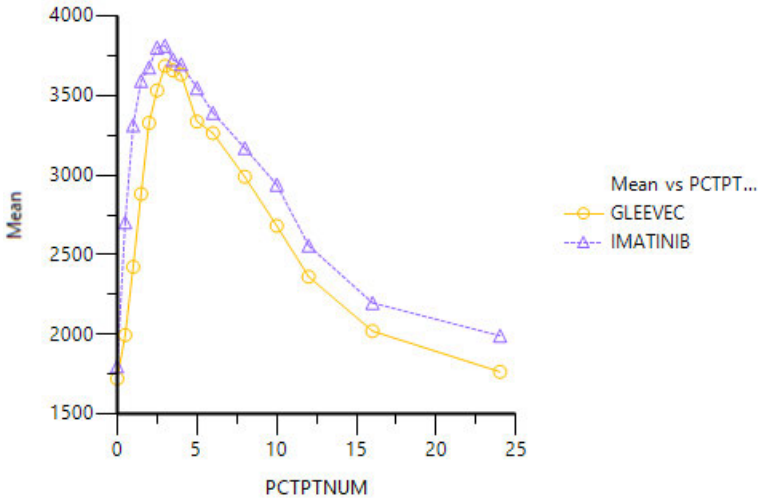


Table 5: Summary statistics for bioequivalence evaluation (excluding site # 252, N=23)

Parameter (unit)	IMKELDI oral solution, 400 mg / 5 ml (Test)	GLEEVEC® 1 x 400 mg (Reference)	GMR of Test / Reference	90% Confidence Interval of GMR
Geometric Mean				
$C_{max,ss}$ (ng/mL)	3858.9	3773.4	102.3	92.7– 112.9
$AUC_{0\text{-}tss}$ (h*ng/mL)	60424.7	56855.3	106.3	95.9- 117.8

Source: Reviewer's analysis

Additional sensitivity analysis in patients meeting the steady state criteria and excluding Site 252 (N=17) also demonstrated a 90% CI of GMR within 80%-125% (data not shown).

3.3.3 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The pivotal bioequivalence study comparing IMKELDI and GLEEVEC® was conducted in the fed status. A food effect study evaluating the bioavailability of IMKELDI in the fasted condition has not been conducted due to concerns with GI irritation. IMKELDI should be administered with food.

No drug-drug interaction studies were conducted with IMKELDI for this application. The dosing instructions with regard to drug-drug interaction will rely on previous data from GLEEVEC®. Specifically, concomitant use of strong CYP3A4 modulators should be avoided and CYP3A4 substrates and CYP2D6 substrates should be used with caution.

3.3.4 *Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?*

The dosing regimen in patients with HI and RI is based on the establishment of a scientific bridge with GLEEVEC®.

4. APPENDICES

4.1 Bioanalytical Method

Imatinib in human plasma was analyzed by tandem mass spectrometry following solid phase extraction. The assay validation parameters are as indicated in Table 6.

Table 6: Validation Parameters for Imatinib assay

Analyte	Imatinib
Assay	Tandem Mass Spectrometry. Solid Phase Extraction
Matrix	K_2 EDTA Human Plasma
Standard Curve	15.014 ng/ml to 8004.7 ng/mL
QC levels	DQC: 16007 ng/mL HQC: 6082.7 ng/mL MQC: 2560.8 ng/mL AQC-1: 1001.3 ng/ml AQC-II: 500.6 ng/ml LQC: 43.6 ng/ml LLOQ QC: 15.0 ng/ml
Recovery	Imatinib: HQC 70.6 %, MQC 69.6 %, LQC 65.6 % IS (Imatinib D8): HQC 68.8 %, MQC 69.1 %, LQC 67.0 %
QC performance:	See nested table below
Selectivity	Blank selectivity and spike selectivity tested in one replicate from each of six individual sources of blank plasma, one 2% hemolyzed plasma and one lipemic plasma. Blank samples were free of interference at the retention times of the analyte(s) and the IS. Spiked samples were within ± 20% LLOQ.
Specificity	2% of 1mg/mL concentration of six OTC/concomitant drug separately spiked in blank and two concentration levels (low and high QCs) of the analyte(s) were processed and quantified under the accepted calibration curve. The mean concentration of the six replicates at each concentration for the plasma sample containing co-med(s) is within ± 15.0% from its nominal value and the precision at each concentration per level is within 15.0%. No interference shown with the blank sample.
Solution stability	25 days at -20°C ± 10°C
Dilution integrity	Dilution QC: 16007 ng/mL; Dilution factor: 1/3rd and 1/5th. % RE -1.2 % and -1.0 %. Precision: 1.3 % and 1.5 %.
Bench-top	16 hrs and 30 mins @ Room temperature
Freeze/Thaw Stability	Freeze Thaw stability up to five Cycles @ -20°C ± 10°C and -70°C ± 15°C
Long-term Stability	245 days at -20°C±10°C and - 70°C±15°C.

	Intra-day		Inter-day	
	accuracy (%)	precision %CV)	accuracy (%)	precision %CV)
HQC	97.7-103.4	0.9-1.4	100.1	2.8
MQC	100.3-107.8	0.9-2.5	102.8	3.9
AQC-1	98-107.5	0.5-1.2	101.9	4.2
AQC-II	95.7-101.4	1.1-1.8	98.5	2.8
LQC	93.2-111.9	1.6-4.1	103	8.2
LLOQ QC	107.3-118	3.0-15.8	112.5	10.4

In Study MW180013, plasma imatinib levels were determined using LC/MS/MS assay as described in Table. Study samples were analyzed in 14 analytical runs. 9.3 % of the study samples were reanalyzed for assigned causes. The maximum duration of frozen storage of study samples (229 days) was within the validated long-term storage duration (245 days when stored at -20°C ± l0°C and -70°C ± 15°C)

Table 7: Summary of in-study assay parameters and performance (Study MW180013)

Analyte	Imatinib
Standard curve performance	Cumulative precision (%CV): 1.9% to 4.6% Cumulative bias range (%bias): -2.4% to 3.0%
QC Performance	Cumulative precision (%CV): 2.4% to 6.5% Cumulative bias range (%bias): -3.8% to 3.0%
Re-assays	9.3% (112 of 1203 samples)
ISR	109/115 (94.8%)
Duration of sample storage	229 days

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