

One Year Post Exclusivity Adverse Event Review: Gleevec (imatinib mesylate)

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1

Outline

- **Background Drug Information**
- **Drug Use Trends**
- **Pediatric Exclusivity Studies**
- **Pediatric Exclusivity Labeling Changes**
- **Additional Relevant Safety Labeling**
- **Adverse Events**
 - Since approval
 - One-year post exclusivity
- **Summary**

2

Background Drug Information

- **Drug:** Gleevec[®] (imatinib mesylate)
- **Therapeutic Category:** protein-tyrosine kinase inhibitor
- **Sponsor:** Novartis
- **Original Market Approval:** May 10, 2001 (capsule) and April 18, 2003 (tablet)
- **Pediatric Exclusivity Granted:** June 9, 2006

3

Background Drug Information

Indications:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive Chronic myeloid leukemia (Ph+CML), chronic phase
- Ph+ CML after failure of interferon alpha (adults and pediatrics) or stem-cell transplant (pediatrics)

Adults only:

- Relapsed or refractory Ph+ acute lymphocytic leukemia (Ph+ ALL)
- Myelodysplastic/myeloproliferative disease
- Aggressive systemic mastocytosis
- Hypereosinophilic syndrome or chronic eosinophilic leukemia
- Metastatic, unresectable or recurrent dermatofibrosarcoma protuberans
- Unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)

Background Drug Information

Dosage in Ph+ CML:

- **Adult patients:**
 - chronic phase: **400 mg/day (maximum 600 mg/day)**
 - accelerated phase or blast crisis: **600 mg (maximum 800 mg)**
 - may be increased based on disease progression or lack of response
- **Pediatric patients (dose may be divided BID):**
 - Newly diagnosed: **340 mg/m²/day (maximum 600 mg)**
 - Prior therapy: **260 mg/m²/day**

5

Labeling: imatinib mesylate

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Glivec safely and effectively. See full prescribing information for Glivec.

GLEEVEC (imatinib mesylate) tablets for oral use
Initial U.S. Approval: 2001

RECENT MAJOR CHANGES

Indications and Usage: CML - Imatinib (1.3), Ph+ ALL (1.4), MDS/MPD (1.5), ASM (1.6), HESCEL (1.7), DWP (1.8), 11/2006

Dosage and Administration: CML - Imatinib (2.1), Ph+ ALL (2.3), MDS/MPD (2.4), ASM (2.5), HESCEL (2.6), DWP (2.7), 11/2006

Warnings and Precautions: Concomitant Heart Failure and Left Ventricular Dysfunction (3.4) 11/2006

INDICATIONS AND USAGE

Glivec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult 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- α therapy (1.3)
- Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after one cell transplant or who are resistant to interferon- α therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival (1.3)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.4)
- Adult patients with myelodysplastic/myeloproliferative disease (MDS/MPD) associated with PPOF (platelet-derived growth factor receptor) gene re-arrangements (1.5)
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation or with c-KIT mutation status unknown (1.6)
- Adult patients with hypomyelopoietic syndrome (HES) and/or chronic neutrophilic leukemia (CEL) who have the FIP1L1-PKDF1a fusion kinase (molecular analysis or FISH demonstration of C/FGF1a/ABL1 deletion) and for patients with HES and/or CEL who are FIP1L1-PKDF1a fusion kinase negative (1.7)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
- Patients with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). The effectiveness of Glivec in GIST is based on objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival (1.9)

DOSE AND ADMINISTRATION

- Adults with Ph+ CML, CP (2.1) 400 mg/day
- Adults with Ph+ CML, AP or BC (2.1) 600 mg/day
- Pediatric with Ph+ CML (2.2) 340 mg/m²/day or 260 mg/m²/day
- Adults with Ph+ ALL (2.3) 600 mg/day
- Adults with MDS/MPD (2.4) 600 mg/day
- Adults with ASM (2.5) 100 mg/day or 400 mg/day
- Adults with HES/CEL (2.6) 100 mg/day or 400 mg/day
- Adults with DWP (2.7) 800 mg/day
- Adults with GIST (2.8) 400 mg/day or 600 mg/day
- Patients with mild to moderate hepatic impairment (2.9) 400 mg/day
- Patients with severe hepatic impairment (2.9) 300 mg/day

All doses of Glivec should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily; whereas a dose of 800 mg should be administered as 400 mg twice a day. Glivec can

be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

DOSE FORMS AND STRENGTHS

Tablets (scored): 100 mg and 400 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus (5.1, 6.1)
- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuresis (5.2, 6.1)
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and, if necessary, transfusion. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter (5.3)
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with cardiovascular and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated (3.4)
- Severe hepatotoxicity may occur. Assess liver function before initiation of treatment and routinely thereafter or as clinically indicated (5.5)
- Grade 3/4 bone marrow has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleed (5.6)
- Gastrointestinal perforation, some fatal, have been reported (5.7)
- Cardiac conduction/heart rate/ventricular dysfunction has been associated with the initiation of Glivec in patients with conditions associated with high systolic blood pressure (e.g., HES, MDS/MPD and ASM) (5.8)
- Rash and dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Glivec (5.9)
- Consider potential toxicity, specifically, liver, kidney, and cardiac toxicity, and immunosuppression from long-term use (5.10)

ADVERSE REACTIONS

The most frequently reported adverse reactions ($\geq 10\%$) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain (5.1, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NOVARTIS PHARMACEUTICALS CORPORATION at 1-888-NOW-NOVA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 inducers may decrease Glivec C_{max} and AUC (2.9, 7.1)
- CYP3A4 inhibitors may increase Glivec C_{max} and AUC (7.2)
- Glivec is an inhibitor of CYP2A6 and may increase the C_{max} and AUC of other drugs (7.3)
- Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin (7.3)
- Systemic exposure to macrolides is expected to increase when co-administered with Glivec (7.5)

USE IN SPECIFIC POPULATIONS

- There is no experience in children less than 2 years of age (4.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

6

Drug Use Trends: imatinib mesylate

Primarily purchased in outpatient pharmacies:

~45% in retail and ~41% mail-order¹

Majority of use in adults

- 99% of retail and mail-order prescriptions²
- 98% of office-based physician visits (July 2005 to June 2006)³

Trend: 4% increase in retail and mail order prescriptions²

- Pre-exclusivity (July 2005 to June 2006): 158, 317
- Post-exclusivity (July 2006 to June 2007): 164, 156

Primary prescribers: hematologists and oncologists³

All surveyed pediatric office visits associated with lymphoproliferative disorder

¹IMS Health, IMS Nationals Sales Perspectives™, Data extracted Aug 2007

²Verispan, LLC, Vector One® National (VONA), Data extracted Aug 2007

³Verispan, LLC, Physician Drug and Diagnosis Audit (PDDA), Data extracted Aug 2007

<http://www.fda.gov/cder/pediatric/Summaryreview.htm>

The screenshot shows the FDA website header with the logo and navigation links. Below the header is a search bar with a 'GO' button and 'powered by Google™'. The search results are titled 'Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies as of July 25, 2007'. It states 'Total Number of Drugs with Summaries Posted: 84'. A table lists the following drugs and their details:

Summaries of Medical and Clinical Pharmacology Reviews			
Glyburide and Metformin - Glucovance	Bristol-Myers Squibb	Medical	Clinical Pharmacology
Imatinib - Gleevec	Novartis	Medical	Clinical Pharmacology
Imiquimod - Aldara	3M	Medical	Clinical Pharmacology
Insulin aspart - NovoLog	Novo Nordisk	Medical	None*

Pediatric Exclusivity Studies: imatinib mesylate

Ph+ CML

- Phase 1 dose finding study, including evaluation of pK with maximum tolerated doses determined for all appropriate age groups
- Phase 2 cytogenetic response

9

Pediatric Exclusivity Study: imatinib mesylate

- Intensive pK sampling, phase 1, n=17
pK in adults and pediatric patients similar
AUC of a 340 mg/m²/day dose comparable to adult dose of 400 mg
- Sparse pK sampling in subset of phase 2 study (n=33)
No significant relationships between measures of exposure and grade ³/₄ toxicities
- Labeling change:
 - 2.2 Pediatric Patients with Ph+ CML (2.0 Dosage and administration)
 - 2.11 Dose Adjustment for Hematologic Adverse Reactions
 - 8.4 Pediatric Use
 - Pharmacokinetic findings described

10

Pediatric Exclusivity Studies: Efficacy imatinib mesylate

- Open label, multicenter, single arm phase 2 study of 340 mg/m²/day in newly diagnosed, untreated patients with CML (n=51)
 - complete hematologic response after 8 weeks: 78%
 - complete cytogenetic response rate (CCyR): 65%
 - partial cytogenetic response (PCyR): 16%
- Open-label, phase 1 study of 260 to 570 mg/m²/day in recurrent CML (n=14)
 - after transplant or resistant to interferon-alpha therapy: CCyR: 7/14 and PCyR 4/14
 - resistant to interferon-alpha: 2/3 achieved CCyR at 242 and 257 mg/m²/day, respectively

11

Labeling Changes: Efficacy of imatinib mesylate

1.3 Pediatric patients with newly diagnosed and recurrent Ph+CML

- **Lack of controlled studies demonstrating clinical benefit (improvement in disease-related symptoms or survival)**

8.4 Pediatric Use

- **Safety and efficacy in newly diagnosed and chronic phase Ph+ CML with recurrence**
- **No data in children < 2 years**
- **Follow-up limited for newly diagnosed**

14.2 Pediatric CML

- **Describes the pediatric exclusivity studies**

12

Pediatric Exclusivity Study: Safety imatinib mesylate (n=54)

No deaths

Grade 3/4 toxicities, primarily hematologic; incidence of myelosuppression higher than adult patients

Non-hematological grade 3/4 : allergic reaction/hypersensitivity, avascular necrosis, rash

Edema/weight gain (14%) low compared with adults (59%)

Abnormal liver function tests (1 case each)

discontinuation: elevated AST/ALT

grade 3/4 increase (autoimmune hepatitis)

Sporadic muscle cramps

No GI hemorrhage

13

Pediatric Exclusivity Study: Safety Labeling Changes imatinib mesylate

5.3 Hematologic Toxicity

- most frequent toxicities: grade 3 or 4 cytopenias

6.4 Adverse Reactions in Pediatric Population:

- safety data based on 93 patients
- overall safety profile similar to adults
- musculoskeletal pain less frequent (20.5%)
- peripheral edema not reported
- nausea and vomiting most commonly reported individual AEs
- incidence of grade 3/4 AEs low

14

Additional Relevant Safety Labeling: imatinib mesylate

5 Warnings and Precautions

- 5.1 Pregnancy: Category D, avoid
- 5.2 Fluid Retention and Edema
- 5.3 Hematologic toxicity
- 5.4 Severe congestive heart failure/ventricular dysfunction
- 5.5 Hepatotoxicity
- 5.6 Hemorrhage
- 5.7 Gastrointestinal disorders
- 5.8 Hyperesosinophilic cardiac toxicity
- 5.9 Dermatologic Toxicities: Steven-Johnson
- 5.10 Toxicities from long term use: hepatic, renal, cardiac & immunosuppression

15

Additional Relevant Safety Labeling: imatinib mesylate

8.1 Pregnancy: Category D (see Warnings)

Adverse Reactions

6.1 Chronic Myeloid Leukemia:

Most frequent: edema, nausea/vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (adults)

16

Adverse Event Reports since Approval (May 10, 2001): imatinib mesylate

Raw counts*	All reports (US)	Serious (US)	Death (US)
All ages	4451 (1970)	4071 (1611)	796 (171)
Adults (≥ 17)	3639 (1628)	3353 (1334)	663 (150)
Pediatrics (0-16)	93 (42)	82 (35)	9 (1)
Unknown Age	719 (310)	636 (232)	124 (20)

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

17

Fatal Adverse Event Reports since Approval (May 10, 2001): imatinib mesylate

8 unduplicated fatal AEs

3 during the one-year post-exclusivity
period

remaining events: highly confounded by
multiple medications, progression of disease, or
complications (e.g., sepsis, pancytopenia)

18

Adverse Event Reports during One-Year Post Exclusivity Period: imatinib mesylate

Raw counts*	All reports (US)	Serious (US)	Death (US)
All ages	908 (334)	898 (326)	194 (44)
Adults (≥ 17)	728 (277)	718 (269)	162 (37)
Pediatrics (0-16)	25 (5)	25 (5)	4 (0)
Unknown Age	908 (334)	898 (326)	194 (44)

19

Adverse Events during Pediatric Exclusivity Period

19 unduplicated cases:

- Fatalities (n=3)
 - maternal exposure (n=1)
- nonfatal AEs
 - maternal exposure (n=2)
 - growth retardation (n=2)
 - remainder highly confounded by multiple medications, progression of disease, or complications (e.g., sepsis, pancytopenia)

20

Fatal Adverse Events during Pediatric Exclusivity Period (n =3, all foreign)

- 13 y/o M with relapsed T-cell ALL after multiple chemo regimens, including “carbocyclines,” multiple antibiotics, and antifungals received imatinib and developed pulmonary edema and cardiac failure, died after multiple cardiac arrests
- 8 y/o F with relapsed Ph+ ALL after cord blood transplantation received imatinib as part of chemo, switched to another regimen died after multi-organ failure, course complicated by aspergillus sepsis and pneumonia
- Multiple congenital anomalies in 30 week preterm infant born to mother treated during first trimester with imatinib for CML, history of consanguinity

21

Nonfatal Adverse Events during Pediatric Exclusivity Period

Gestational Exposure (n=3)

Fatal case with multiple anomalies, previously described

Healthy preterm infant (35 week)

Term female infant with hypoplastic thumb (first trimester exposure to imatinib; persistent exposure interferon alfa-2B and Anti-D immunoglobulin)

Labeling: 8.1 Pregnancy: women of childbearing age avoid pregnancy, use contraception

22

Unlabeled Non Fatal Adverse Events during Pediatric Exclusivity Period

13 y/o F with Ph+ ALL developed biopsy proven retroperitoneal fibrosis with bilateral hydronephrosis and ureteric obstruction after 3 months of therapy

9 y/o F with ALL on imatinib, vincristine and doxorubicin for ~2 weeks developed hyponatremia, hypertension and seizures and posterior encephalopathy syndrome (MRI), improved with sodium correction, BP control and phenobarbital

Labeling: 5.10 long term toxicity: renal

6.12 Additional data from Multiple Clinical Trials:

hypertension (infrequent), hyponatremia (rare), convulsion (rare)

23

Unlabeled Non Fatal Adverse Events during Pediatric Exclusivity Period

10 y/o M with gastrointestinal stromal tumor became grey and developed spots, growth deprivation and cold hands and feet.

5+ y/o M with CML diagnosed at age 2 treated with imatinib for 4 to 5 years when growth retardation was noted

Berman E, Nicolaidis M, Maki R, et al. Altered bone and mineral metabolism in patients receiving imatinib mesylate. *NEJM* 2006; 354(19): 2006-2013

24

Summary: imatinib mesylate

- Labeling updated with new pediatric indication
- AEs incorporated: higher incidence of myelosuppression and less peripheral edema, but otherwise comparable to adults
- No new pediatric AEs identified during one-year exclusivity period
- The FDA recommends routine monitoring of imatinib for AEs in all populations

Does the Advisory Committee concur?

25

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26