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

Pediatric Advisory Committee Meeting
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Food and Drug Administration

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
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

### 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

Labeling: imatinib mesylate

- **INDICATIONS AND USAGE:**
  - Imatinib is used for the treatment of patients with chronic myelogenous leukemia (CML) in chronic phase.
  - It is also used for the treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

- **DOSAGE AND ADMINISTRATION:**
  - **Adults:**
    - 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

- **CONTRAINDICATIONS:**
  - Imatinib should not be used in patients with active or untreated variceal bleeding, severe gastrointestinal ulcer disease, or other significant organ malformations or systemic congenital defects.

- **WARNINGS AND PRECAUTIONS:**
  - Patients with moderate or severe liver function impairment (Child-Pugh Class B or C) should not be treated with imatinib.

- **ADVERSE REACTIONS:**
  - Common adverse reactions include:
    - Gastrointestinal: nausea, vomiting, anorexia, abdominal pain, diarrhea, constipation, flatulence
    - Hematologic: neutropenia, anemia, thrombocytopenia
    - Skin: rash, pruritus

- **DRUG INTERACTIONS:**
  - Imatinib is a substrate of the cytochrome P450 3A4 system and is not an inducer or inhibitor of this system. Other drugs that are substrates of this system may affect the plasma concentration of imatinib.

- **NURSING CONSIDERATIONS:**
  - Patients should be monitored for evidence of gastrointestinal bleeding and should be advised to report any signs of bleeding.

- **PREGNANCY:**
  - Imatinib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- **LACTATION:**
  - It is unknown if imatinib is excreted in breast milk. Women who are breastfeeding should not use imatinib.

- **REPRODUCTIVE TOXICITY:**
  - Imatinib may impair fertility in both men and women. Men should not father children while taking imatinib and should use effective contraception during treatment.

- **PATIENT CONTINUING INSTRUCTIONS:**
  - Patients should be advised to continue taking imatinib as long as it is effective and tolerated.

- **SUPPLEMENTAL INFORMATION:**
  - For detailed instructions, see the package insert that accompanies the drug.
Drug Use Trends: imatinib mesylate

Primarily purchased in outpatient pharmacies:
~45% in retail and ~41% mail-order\(^1\)

Majority of use in adults
- 99% of retail and mail-order prescriptions\(^2\)
- 98% of office-based physician visits (July 2005 to June 2006)\(^3\)

Trend: 4% increase in retail and mail order prescriptions\(^2\)
- Pre-exclusivity (July 2005 to June 2006): 158, 317
- Post-exclusivity (July 2006 to June 2007): 164, 156

Primary prescribers: hematologists and oncologists\(^3\)

All surveyed pediatric office visits associated with lymphoproliferative disorder

\(^1\)IMS Health, IMS Nationals Sales Perspectives\(\text{™}\), Data extracted Aug 2007
\(^2\)Verispan, LLC, Vector One\(\text{®}\) National (VONA), Data extracted Aug 2007
\(^3\)Verispan, LLC, Physician Drug and Diagnosis Audit (PDDA), Data extracted Aug 2007

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

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 ¾ 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
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

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
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

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
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

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

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

*includes duplicates and unknown ages

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

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

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</thead>
<tbody>
<tr>
<td>All ages</td>
<td>908 (334)</td>
<td>898 (326)</td>
<td>194 (44)</td>
</tr>
<tr>
<td>Adults (≥ 17)</td>
<td>728 (277)</td>
<td>718 (269)</td>
<td>162 (37)</td>
</tr>
<tr>
<td>Pediatrics (0-16)</td>
<td>25 (5)</td>
<td>25 (5)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Unknown Age</td>
<td>908 (334)</td>
<td>898 (326)</td>
<td>194 (44)</td>
</tr>
</tbody>
</table>

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)
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

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
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)

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

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?

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