FDA Databases 101 for Clinical Pharmacologists

Anuradha Ramamoorthy, Ph.D.
Reviewer, Genomics and Targeted Therapy Group
Office of Clinical Pharmacology
OTS/CDER/OMPT/FDA

Science at Sunrise March 17, 2017

Disclaimer: This speech reflects the views of the speaker and should not be construed to represent FDA’s policies
Agenda

- FDA Databases
- FAERS
- FDA Pharmacogenomic Biomarkers Table
- precisionFDA Portal
Agenda

FDA Databases

- FAERS
- FDA Pharmacogenomic Biomarkers Table
- precisionFDA Portal
FDA Databases

Drug Approvals and Databases

Database Examples

- Orange Book
- Labeling Search
- Postmarketing Requirements and Commitments
- Postmarket Drug Safety Information for Patients and Providers
- List of Qualified Biomarkers
- Drugs@FDA
FDA Databases

Medical Device Databases

Database Examples

- Premarket Approval (PMA)
- List of Cleared or Approved Companion Diagnostic Devices
- Nucleic Acid Based Tests
Agenda

- FDA Databases
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FDA Adverse Event Reporting System

About FAERS
The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Learn more
General information
Learn more about FDA Adverse Event Reporting System

Provider
FDA

License
Public Domain and CC0

Updates
Frequency Quarterly
Lag in data updates 3 months

Time period
The files listed on this page contain raw data extracted from the AERS database for the indicated time ranges and are not cumulative.

Users of these files need to be familiar with creation of relational databases using applications such as ORACLE®, Microsoft Office Access, MySQL® and IBM DB2 or the use of ASCII files with SAS® analytic tools.

A simple search of FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases. However, you can get a summary FAERS report for a product by sending a Freedom of Information Act (FOIA) request to FDA. You can also request individual case reports by submitting a FOIA request listing case report numbers.

- General Instructions on How to Make a FOIA Request
- Instructions for Requesting Individual Case Reports

The quarterly data files, which are available in ASCII or SGML formats, include:

- demographic and administrative information and the initial report image ID number (if available);
- drug information from the case reports;
- reaction information from the reports;
- patient outcome information from the reports;
- information on the source of the reports;
- a "README" file containing a description of the files.

For assistance, please email the FDA/CDER Office of Surveillance and Epidemiology, Division of Medication Errors and Technical Support: cdrorsetracking@fda.hhs.gov.
FDA Adverse Event Reporting System

FAERS Data Files

Click on a Link Below to Begin Downloading

- FAERS ASCII 2016q3 (ZIP - 40.6MB)
  July - September 2016
- FAERS XML 2016q3 (ZIP - 76.9MB)
  July - September 2016
- FAERS ASCII 2016q2 (ZIP - 42.3MB)
  April - June 2016
- FAERS XML 2016q2 (ZIP - 68.9MB)
  April - June 2016
- FAERS ASCII 2016q1 (ZIP - 43.7MB)
  January - March 2016
- FAERS XML 2016q1 (ZIP - 71.5MB)
  January - March 2016
- FAERS ASCII 2015q4 (ZIP - 39.7MB)
  October - December 2015
- FAERS XML 2015q4 (ZIP - 65.8MB)
  October - December 2015
- FAERS ASCII 2015q3 (ZIP - 44.7MB)
  July - September 2015
- FAERS XML 2015q3 (ZIP - 73.3MB)
  July - September 2015
- FAERS ASCII 2015q2.zip (ZIP - 36.4MB)
  April - June 2015
How is FAERS Used?

Literature Examples From PubMed

FAERS data have certain limitations (refer to FAERS webpage for details)

1. Can Disproportionality Analysis of Post-marketing Case Reports be Used for Comparison of Drug Safety Profiles?
   Michel C, Scosyrev E, Petrin M, Schmouder R.
   PMID: 28224371
   Similar articles

   Hauben M, Hung E, Hsieh WY.
   PMID: 28203363 Free PMC Article
   Similar articles

   Rahman MM, Scalesa MJ, Hansen RA.
   PMID: 28166651
   Similar articles

4. Validation of New Signal Detection Methods for Web Query Log Data Compared to Signal Detection Algorithms Used With FAERS.
   PMID: 28155508
   Similar articles

5. Angiotensin receptor blockers and the risk of cancer: data mining of a spontaneous reporting database and a claims database.
   Fujimoto M, Kanou M, Hosomi K, Takada M.
   PMID: 28079518
   Similar articles

6. Adverse event detection using the FDA post-marketing drug safety surveillance system: Cardiotoxicity associated with loperamide abuse and misuse.
   Swank KA, Wu E, Kortepeter C, McAninch J, Levin RL.
Agenda

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Table of Pharmacogenomic Biomarkers in Drug Labeling

• What is it?
A comprehensive regulatory scientific database that contains pharmacogenomic (PGx) information derived from CDER approved drug products from 1906 to present

• Where can you find it?
Link: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
### Drug Labels

PharmGKB annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency, Japan (PMDA) and Health Canada (Santé Canada) (HCSC). PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. A list of genes and phenotypes found within the label is mapped to label section headers and listed at the end of each annotation. PharmGKB also attempts to interpret the level of action implied in each label with the "PGx Level" tag.

See the legend for more information about drug label sources, which labels are selected for annotation and PGx Levels:

We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA, PMDA, HCSC or other Medicine Agencies around the world - please contact feedback.

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>EMA</th>
<th>PMDA</th>
<th>HCSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>B Genetic testing required</td>
<td>Genetic testing required</td>
<td></td>
<td>Genetic testing required</td>
</tr>
<tr>
<td>abiraterone</td>
<td>Informative PGx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acetaminophen</td>
<td></td>
<td></td>
<td>Actionable PGx</td>
<td></td>
</tr>
<tr>
<td>afatinib</td>
<td>B Genetic testing required</td>
<td>Genetic testing required</td>
<td>Genet...</td>
<td>Genetic testing required</td>
</tr>
<tr>
<td>afutuzumab</td>
<td>B Informative PGx</td>
<td></td>
<td></td>
<td>Informative PGx</td>
</tr>
<tr>
<td>alec...</td>
<td>B Genetic testing required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alirocumab</td>
<td>B Actionable PGx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aliskiren</td>
<td>Informative PGx</td>
<td></td>
<td></td>
<td>Informative PGx</td>
</tr>
<tr>
<td>allopurinol</td>
<td></td>
<td>Actionable PGx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amitriptyline</td>
<td></td>
<td></td>
<td></td>
<td>Actionable PGx</td>
</tr>
</tbody>
</table>
Live Demo

Table of Pharmacogenomic Biomarkers in Drug Labeling

Link to back up slides
Agenda

FDA Databases

FAERS

FDA Pharmacogenomic Biomarkers Table

precisionFDA Portal
FDA created **precisionFDA**, a community research and development portal to allow for testing, piloting, and validating existing and new bioinformatics approaches to NGS processing.

Courtesy: Elaine Johanson
What is precisionFDA?

**PrecisionFDA** is an externally focused cloud based portal that engages a community of over 2,500 users across the world. It allows researchers to experiment, share data and tools, and collaborate to help define standards for evaluating analytical pipelines.

Courtesy: Elaine Johanson
precisionFDA and the Community

precisionFDA provides...

- Resources for computation and storage for advancement of regulatory science
- Community challenges
- A library of reference material, tools, etc. including community contributions such as:
  - GA4GH VCF comparison tool
  - BWA-MEM mapper
  - GATK 3.5 licensed to precisionFDA
  - VarSim simulator
  - RTG Core 3.7 + RTG Tools 3.6
  - NA12878 NIST, Garvan, and Platinum Genome sequences
- Ability to “dockerize” applications for ease of use, transportability and consistency in performance across platforms

Members include...

- NGS-based test providers
- Standards-making bodies
- Pharmaceutical & biotechnology companies
- Healthcare providers
- Academic medical centers
- Research consortia
- Government agencies

Courtesy: Elaine Johanson
How to Join the precisionFDA Community?

Step 1: Go to https://precision.fda.gov

Step 2: Request access and receive browse capability and instructions on how to obtain approval to be a full contributor and member of the precisionFDA community

Step 3: Request contributor access

Step 4: Set up two factor authentication

Step 5: Start working with experts from around the world to help move regulatory science forward

Courtesy: Elaine Johanson
precisionFDA

Courtesy: Elaine Johanson
PrecisionFDA Challenges

Participate in our challenges to engage with and contribute to the community

**App-a-thon in a Box**
- 28 responses
- 79 followers
  - Challenge started: 31 Aug 2016 12:00 UTC
  - Submissions closed: 31 Dec 2016 23:59 UTC
  - Results announced: 04 Jan 2017 22:10 UTC

**Truth Challenge**
- 25 responses
- 58 followers
  - Challenge started: 27 Apr 2016 03:59 UTC
  - Submissions closed: 27 May 2016 03:59 UTC
  - Results announced: 29 Jun 2016 13:30 UTC

**Consistency Challenge**
- 17 responses
- 54 followers
  - Challenge started: 26 Feb 2016 03:59 UTC
  - Submissions closed: 26 Apr 2016 03:59 UTC
  - Results announced: 26 May 2016 00:50 UTC

Courtesy: Elaine Johanson
precisionFDA

• Coming Soon...
  • Ask questions of our Expert of the Month – Early Spring 2017
  • Perform comparisons utilizing the new and improved GA4GH Comparator Tool – Spring 2017
  • Participate in a new precisionFDA Challenge – Summer 2017

• Questions? Reach out via email to the precisionFDA team: precisionFDA@fda.hhs.gov
• Tip: Checkout YouTube videos by UCSF-Stanford CERSI

Courtesy: Elaine Johanson
Summary

FDA Databases

FAERS

FDA Pharmacogenomic Biomarkers Table

precisionFDA Portal
Acknowledgements

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  - Anuradha Ramamoorthy, PhD
  - Kate Drozda, PharmD
  - Jielin Sun, PhD
  - Oluseyi Adeniyi, PharmD, PhD

- precisionFDA
  - precisionFDA Project Manager Elaine Johanson
Questions?
Backup
Agenda

- FDA Databases
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- precisionFDA Portal
# Table of Pharmacogenomic Biomarkers in Drug Labeling

A snapshot:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Labeling Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Infectious Diseases</td>
<td>HLA-B*57:01</td>
<td>Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions</td>
</tr>
<tr>
<td>Ado-Trastuzumab Emtansine</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Endocrinology</td>
<td>Not specified</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Oncology</td>
<td>ESR1, PGR</td>
<td>Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies</td>
</tr>
<tr>
<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYF2D6</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
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<tr>
<td>Aripiprazole Lauroxil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
</tr>
<tr>
<td>Arsenic Trioxide</td>
<td>Oncology</td>
<td>PML-RARA</td>
<td>Indications and Usage</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
</tbody>
</table>
Table of Pharmacogenomic Biomarkers in Drug Labeling

• What is included in the Table?

  PGx biomarkers, including but are not limited to, germline or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities. Selected protein biomarkers (e.g., used for patient selection) may also be included.

  Consistent with ICH E15

• What is the source of information?
  – CDER approved product labeling found at Drugs@FDA website
    • Newly approved products
    • Labeling updates for previously approved products

• How often is the Table updated?
  Every 6 months*
Table of Pharmacogenomic Biomarkers in Drug Labeling

• Where is PGx information found in the labeling for inclusion in the Table?
  Commonly found in sections:
  – 1: Indications and Usage
  – 2: Dosage and Administration
  – 4: Contraindications
  – 5: Warnings and Precautions
  – 12: Clinical Pharmacology, and
  – 14: Clinical Studies

• What are the inclusion criteria?
  PGx biomarker content in labeling may be related to the following:
  – Drug exposure and clinical response variability
  – Risk for adverse events
  – Dosing
  – Mechanisms of drug action
  – Trial design features
  – Certain exclusion criteria apply*
# Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Labeling Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinatumomab</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Clinical Studies</td>
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<tr>
<td>Bosutinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
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<tr>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
</tr>
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<td>Imatinib (2)</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
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<tr>
<td>Nilotinib (1)</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
</tr>
<tr>
<td>Omacetaxine</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
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<tr>
<td>Dasatinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome); T315I mutation</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
</tr>
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<td>Ponatinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome); T315I mutation</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
</tr>
</tbody>
</table>
Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Labeling Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Oncology</td>
<td>KIT</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
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<td>(1)</td>
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<tr>
<td>Imatinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
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<tr>
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<td>Oncology</td>
<td>PDGFRB</td>
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<tr>
<td>Imatinib</td>
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<td>FIP1L1-PDGFR A</td>
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</table>
### Drugs@FDA: FDA Approved Drug Products

**New Drug Application (NDA):** 021588  
**Company:** NOVARTIS  
**Drug Name(s):**  
- GLEEVEC (IMATINIB MESYLATE)

**Other Important Information from FDA**

- **Products on NDA 021588**
- **Approval Date(s) and History, Letters, Labels, Reviews for NDA 021588**
- **Labels for NDA 021588**
- **Therapeutic Equivalents for NDA 021588**
Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

<table>
<thead>
<tr>
<th>Action Date</th>
<th>Submission</th>
<th>Submission Classification or Approval Type</th>
<th>Letters, Reviews, Labels, Patient Package Insert</th>
<th>Note</th>
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<tbody>
<tr>
<td>09/27/2016</td>
<td>SUPPL-47</td>
<td>Labeling</td>
<td>Label (PDF)</td>
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<tr>
<td>08/25/2016</td>
<td>SUPPL-46</td>
<td>Labeling</td>
<td>Label (PDF)</td>
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<tr>
<td>08/25/2016</td>
<td>SUPPL-45</td>
<td>Efficacy</td>
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<td>01/30/2015</td>
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<td>Label (PDF)</td>
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</tr>
</tbody>
</table>
Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GLEEVEC safely and effectively. See full prescribing information for GLEEVEC.

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

----------------------RECENT MAJOR CHANGES----------------------
Indications and Usage (1.1, 1.2, 1.3) /8/2016
Dosage and Administration (2.1, 2.2, 2.3) /8/2016
Warnings and Precautions (3.10, 2.1, 2.2) /8/2016

INDICATIONS AND USAGE:
Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (1.1).
- 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 (1.2).
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3).
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy (1.4).
- Adults with myeloproliferative/myelodysplastic diseases (MDM/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangement as determined by an FDA-approved test (1.5).
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation as determined by an FDA-approved test or with c-KIT mutational status unknown (1.6).
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (molecular analysis or FISH demonstration of CHIC3 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown (1.7).
- Adult patients with unresectable, recurrent and/or metastatic gastrointestinal stromal tumors (GIST) (1.8).
- Patients with Kit (CD117) positive unresectable and/or metastatic gastrointestinal stromal tumors (CD117) (1.9).
- Adjunctive treatment of adult patients following resection of Kit (CD117) positive GIST (1.10).

Dosage and Administration:
- Adults with Ph+ CML CP (2.2): 400 mg/day.
- Adults with Ph+ CML AF or BC (2.2): 600 mg/day.
- Pediatric with Ph+ CML CP (2.3): 340 mg/m²/day.
- Adults with Ph+ ALL (2.4): 600 mg/day.
- Pediatric with Ph+ ALL (2.5): 340 mg/m²/day.
- Adults with MDS/MPD (2.6): 400 mg/day.
- Adults with ASAT (2.7): 100 mg/day or 400 mg/day.
- Adults with HES/CEL (2.8): 100 mg/day or 400 mg/day.
- Adults with DFSP (2.9): 600 mg/day.
- Adults with metastatic and/or unresectable GIST (2.10): 400 mg/day.
- Adjunctive treatment of adults with GIST (2.11): 400 mg/day.
- Patients with mild to moderate hepatic impairment (2.12): 400 mg/day.
- Patients with severe hepatic impairment (2.12): 200 mg/day.

All doses of Gleevec should be taken with a meal and a large glass of water.

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-609-6652 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS:
- CYP3A4 inducers may decrease Gleevec Cmin and AUC (2.12, 7.1, 12.3).
- CYP3A4 inhibitors may increase Gleevec Cmin and AUC (7.2, 12.3).
- Gleevec is an inhibitor of CYP3A4 and CYP2D6 which may increase the Cmin and AUC of other drugs (7.3, 7.4, 12.3).
- Patients who require anticoagulation should receive a low-molecular weight or standard heparin and not warfarin (7.5).

See 17 for PATIENT COUNSELING INFORMATION.
Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

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**INDICATIONS AND USAGE**

Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with **Philadelphia chromosome positive** chronic myeloid leukemia (Ph+ CML) in chronic phase (1.1)
- 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 (1.2)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3)
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy (1.4)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test (1.5)
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown (1.6)
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown (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) (1.9)
- Adjuvant treatment of adult patients following resection of **Kit (CD117) positive** GIST (1.10)
<table>
<thead>
<tr>
<th>Category</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with Ph+ CML CP (2.2)</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Adults with Ph+ CML AP or BC (2.2)</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Pediatrics with Ph+ CML CP (2.3)</td>
<td>340 mg/m²/day</td>
</tr>
<tr>
<td>Adults with Ph+ ALL (2.4)</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Pediatrics with Ph+ ALL (2.5)</td>
<td>340 mg/m²/day</td>
</tr>
<tr>
<td>Adults with MDS/MPD (2.6)</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Adults with ASM (2.7)</td>
<td>100 mg/day or 400 mg/day</td>
</tr>
<tr>
<td>Adults with HES/CEL (2.8)</td>
<td>100 mg/day or 400 mg/day</td>
</tr>
<tr>
<td>Adults with DFSP (2.9)</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Adults with metastatic and/or unresectable GIST (2.10)</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Adjuvant treatment of adults with GIST (2.11)</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Patients with mild to moderate hepatic impairment (2.12)</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Patients with severe hepatic impairment (2.12)</td>
<td>300 mg/day</td>
</tr>
</tbody>
</table>
Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Referenced Subgroup‡</th>
<th>Labeling Sections‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinatumomab</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome negative</td>
<td>Indications and Usage, Clinical Studies</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome negative</td>
<td>Clinical Studies</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome positive</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
</tr>
<tr>
<td>Imatinib (2)</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome positive</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Nilotinib (1)</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome positive</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Omacetaxine</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome positive</td>
<td>Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome positive, T315i mutation positive</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Oncology</td>
<td>BCR-ABL1</td>
<td>Philadelphia chromosome</td>
<td>Indications and Usage,</td>
</tr>
</tbody>
</table>
Biomarkers and Genetic Factors in Product Labeling

198 gene-drug pairs
163 drugs, 54 biomarkers*
43% metabolism/transport
34% target/pathway
23% immunologic/other safety

92 actionable**
Otherwise, descriptive of study design feature or presence/absence of gene-drug interaction

* Includes some products with multiple drugs and families of biomarkers resulting in a phenotype (e.g. urea cycle disorders)
** Management recommendations excluding “use with caution”

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