

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

RCM#: 2007-202

DATE: August 15, 2007

TO: Lisa L. Mathis, M.D., Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
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Office of Pediatric Therapeutics (OPT), OC

FROM: Jennifer Steele, Pharm.D., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Imatinib mesylate (Gleevec®)
Pediatric Exclusivity Approval Date: 6/9/2006

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of imatinib in pediatric patients. Up to the "data lock" date of July 9, 2007, AERS contained 4451 cases for imatinib (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 2% of the total (93/4451).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, June 9, 2006 to June 9, 2007. We used an AERS data lock date of July 9, 2007 to allow time for reports received up to June 9, 2007 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 908 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 3% of the total number of cases (25/908). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

2. Products, Indications, Pediatric Labeling, Pregnancy Category and Labeling, and Pediatric Filing History

2.1 Products

Imatinib is supplied in the U.S. as:

- 100mg oral tablet
- 400mg oral tablet

2.2 Approved Indications

Imatinib is approved in the U.S. for the treatment of:

- Newly diagnosed adult patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- Patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- Pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy.
- Adult patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL).
- Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR gene rearrangements.
- Adult patients with aggressive systemic mastocytosis 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-PDGFR α fusion kinase and for patients with HES and/or CEL who are FIP1L1-PDGFR α 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.

2.3 Pediatric Labeling

The labeling for imatinib includes the following information concerning pediatric patients.

Clinical Pharmacology

Special Populations, Pediatric: As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m² in children vs. 10.0 L/hr/m² in adults), as was the half-life (14.8 hours in children vs. 17.1 hours in adults). Dosing in children at 260 mg/m² and 340 mg/m² achieved an AUC similar to the 400-mg dose in

adults. The comparison of $AUC_{(0-24)}$ on Day 8 vs. Day 1 at 260 mg/m² and 340 mg/m² dose levels revealed a 1.5- and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increased dose.

Clinical Studies

Pediatric CML: A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicenter, single arm phase 2 trial. Patients were treated with Gleevec 340 mg/m²/day, with no interruptions in the absence of dose limiting toxicity. Complete hematologic response (CHR) was observed in 78% of patients after 8 weeks of therapy. The complete cytogenetic response rate (CCyR) was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (pCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 6.74 months.

One open-label, single-arm study enrolled 14 pediatric patients with Ph⁺ CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients ranged in age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were > 18 years old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had a minimal cytogenetic response.

In a second study, 2 of 3 patients with Ph⁺ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.

Precautions

Hematologic Toxicity: In pediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy.

Pediatric Use: Gleevec safety and efficacy have been demonstrated in children with newly diagnosed Ph⁺ chronic phase CML and in children with Ph⁺ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon-alpha therapy. There are no data in children under 2 years of age. Follow-up in children with newly diagnosed Ph⁺ chronic phase CML is limited.

Adverse Reactions

Adverse Reactions in Pediatric Population: The overall safety profile of pediatric patients treated with Gleevec in 93 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting were the most commonly reported individual AEs with an incidence similar to that seen in adult patients. Although most patients experienced AEs at some time during the study, the incidence of Grade 3/4 AEs was low.

2.4 Pregnancy Category and Labeling

Imatinib is pregnancy category D. The labeling includes the following information related to pregnancy.

Warnings, Pregnancy

Women of childbearing potential should be advised to avoid becoming pregnant.

Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses ≥ 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day based on body surface area. Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered doses ≥ 45 mg/kg (approximately one-half the maximum human dose of 800 mg/day based on body surface area) also experienced significant post-implantation loss as evidenced by either early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum Days 0 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤ 30 mg/kg (one-third the maximum human dose of 800mg).

Male and female rats were exposed in utero to a maternal imatinib mesylate dose of 45 mg/kg (approximately one-half the maximum human dose of 800mg) from Day 6 of gestation and through milk during the lactation period. These animals then received no imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male and female animals were then mated.

There are no adequate and well-controlled studies in pregnant women. If Gleevec (imatinib mesylate) is used during pregnancy, or if the patient becomes pregnant while taking (receiving) Gleevec, the patient should be apprised of the potential hazard to the fetus.

2.5 Filing History

A formal Written Request (WR) for pediatric studies of imatinib was issued to Novartis Pharmaceuticals Corporation on September 20, 2000. Amendments were made to the WR on May 28, 2003 and October 26, 2004 and the WR was reissued on July 2, 2002 and May 10, 2004. The sponsor completed the following studies:

- A phase 1 dose finding study, including evaluation of pharmacokinetics, with maximum tolerated doses determined for all appropriate age groups.
- A phase 2 study to determine STI571 activity in pediatric patients with Philadelphia positive leukemia.

These studies fulfilled the requirements of the WR and pediatric exclusivity was granted June 9, 2006. A supplemental new drug application was submitted March 27, June 6, July 7, and September 25, 2006 to provide for the use of Gleevec for newly diagnosed Philadelphia positive CML in pediatric patients. This application was approved September 27, 2006.

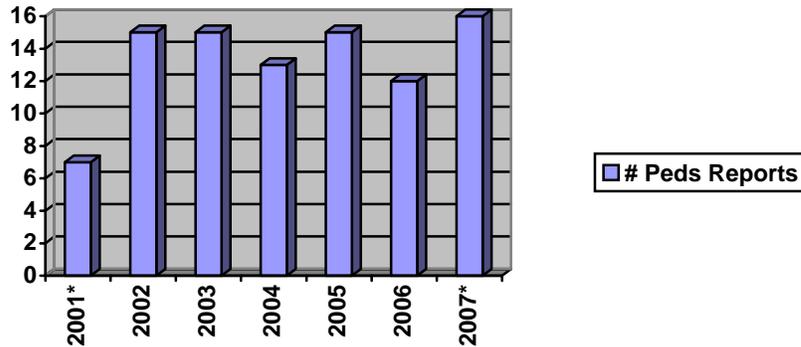
3. AERS Search Results: Imatinib

3.1 Count of Reports: AERS Search including all sources - U.S. & Foreign from Marketing Approval Date (Table 1).

Table 1. Crude counts ¹ of AERS Reports for All Sources from Marketing Approval Date (May 10, 2001 to July 9, 2007; US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	3639 (1618)	3353 (1334)	663 (150)
Pediatrics (0-16 yrs.)	93 (42)	82 (35)	9 (1)
Age unknown (Null values)	719 (310)	636 (232)	124 (20)
Total	4451 (1970)	4071 (1611)	796 (171)

¹ May include duplicates.
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

Figure 1. Reporting trend for pediatric reports from approval date.



*Data from approval date to data lock date, not inclusive of entire year.

3.2 Count of Reports: AERS Search including all sources - U.S. & Foreign from Pediatric Exclusivity Approval Date (Table 2).

Table 2. Crude counts ¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (June 9, 2006 to July 9, 2007; US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs)	728 (277)	718 (269)	162 (37)
Pediatrics (0-16 yrs)	25 (5)	25 (5)	4 (0)
Age unknown (Null Values)	155 (52)	155 (52)	28 (7)
Total	908 (334)	898 (326)	194 (44)

¹ May include duplicates.
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the Pediatric Exclusivity Period.

Nineteen unduplicated pediatric reports, including three unduplicated pediatric reports following gestational exposure to imatinib, were received during the pediatric exclusivity period.

4.1 Case Characteristics

Table 3 below describes the characteristics of the nineteen pediatric cases reported during the pediatric exclusivity period.

Table 3. Characteristics of pediatric cases* reported during the pediatric exclusivity period (June 9, 2006 to July 9, 2007) n=19	
Gender [n=18]	Male: 10 Female: 8
Age [n=19]	0- <1 month: 3 1 month - 2 yrs: 0 3-5 yrs: 2 6-11 yrs: 7 12-16 yrs: 7 Median: 10 years; Mean: 8.5 years; Range 0 to 15 years
Origin [n=19]	U.S.: 4 Foreign: 15
Daily dose [n=13]	200mg: 1 300mg: 3 400mg: 8 450mg: 1
Time to onset of event (1 st dose to event) [n=13]	Median: 42 days; Mean: 257 days Range: 3 days to 4 years
Indications [n=18]	ALL: 10 CML: 6 GIST: 1 CLL: 1
Outcomes [n=19]	Death 3, Hospitalization 8 Disability 2, Congenital Anomaly 2, Other 10

*For cases of gestational exposure, maternal dose, approximate length of gestational exposure, and maternal indication are listed.

4.2 Summary of Fatal Cases received during the Pediatric Exclusivity Period.

There were 3 fatal pediatric cases received during the pediatric exclusivity period (unlabeled events are underlined).

ISR# 5313305-7, Greece

A 13 year old male was diagnosed with T-acute lymphoblastic leukemia May 9, 2005. He started treatment with “Alb-BFM-95 Protocol IFR”. After medullary relapse on June 9, 2006, he received two regimens of “Ida-FLA6” (6/14/06, 8/13/06) and “Campath LH” (6/21/06). After failure of “many” other treatments (including “high doses of carbocyclines”), Gleevec 200mg BID was initiated 7/3/2006. On 9/12/2006, the patient

presented with pulmonary edema and non-responsive cardiac failure. Concomitant medications included Zovirax, Losec, V-feud, Spetrin, ciprofloxacin, G-CSF, Primperan, Targocid, Briklin, Synercid, Zyvox, and Ambisome. Multiple episodes of cardiac arrests lead to the patient's death on [redacted]. The treating physicians considered this case "a rare case and cannot assess causality with Gleevec treatment, but rather with high doses of carbocyclines".

ISR# 5269992-5, Japan

An 8 year old female was diagnosed with Philadelphia chromosome positive ALL at the age of 6. She underwent allogeneic cord blood transplantation five months after disease onset. Eight months after transplantation, her ALL relapsed. She was then started on Gleevec, dexamethasone, vincristine, and cyclophosphamide (for an unspecified time). Therapy was then changed to cytarabine, idarubicin, and ifosfamide. Remissions could not be achieved. The case was further complicated by neutropenia, pyrexia, and Aspergillus sepsis and pneumonia¹. The patient died of on the 302nd day of illness of multi-organ failure.

ISR# 5345221-9, Germany

This is a report of a baby following gestational exposure to Gleevec. The mother had been treated with Gleevec 400mg daily for CML since 7/1/2000. She became pregnant in 9/2005 and Gleevec was discontinued 10/11/2005. Of note, the baby's parents were first degree relatives. An ultrasound revealed intense deformities of the baby including hydrocephaly communicative, hypoplasia cerebellar, spastic posture of the body, large atrial septum defect with overriding aorta, ascites, pericardial effusion, and skin edema. In week 30 of pregnancy, the mother's amniotic sac ruptured and the baby was delivered. The baby died 30 minutes after delivery due to congenital malformation of the heart cavities and connecting structures. The physician assessed the causality between all events, baby's death, and Gleevec as probable.

4.3 Summary of Non-fatal cases received during the Pediatric Exclusivity Period.

The following pediatric cases describing unlabeled events were received during the pediatric exclusivity period (unlabeled events are underlined). Please see Table 4 for details of all non-fatal cases (labeled and unlabeled events)².

ISR# 5057157-1, United Kindom, Retroperitoneal fibrosis/Hydronephrosis

A 13 year old female was enrolled in an open-label phase II/III study of imatinib with chemotherapy (dates/name of therapy not provided) in children with Ph+ ALL. She received imatinib from 3/14/2005 to 5/16/2005. On [redacted] her creatinine was 109 (units not reported). An abdominal CT scan and ultrasound showed evidence of retroperitoneal fibrosis with bilateral hydronephrosis and ureteric obstruction (diagnosis confirmed by biopsy on [redacted]). The patient then underwent bilateral ureteric stent

¹ Sepsis and pneumonia are labeled events for Gleevec; *Aspergillus* sepsis and *Aspergillus* pneumonia are unlabeled for Gleevec.

² Two additional non-fatal cases of infants following gestational exposure to Gleevec are described in section 4.4.

placement. She subsequently developed increased blood pressure that was treated with hydralazine and nifedipine. The case was further complicated by the development of pleural effusions. The patient responded well to ureteric stenting and her renal function returned to normal.

ISR#s 5095088-1 and 5073487-1 (duplicate with additional detail), Japan, Posterior reversible encephalopathy syndrome

A 9 year old female was treated with Gleevec (5/2 - 5/16/2006), vincristine (5/1 – 5/8/2006), and doxorubicin (5/1/2006) for ALL. The patient experienced hyponatremia and hypertension (5/15/2006) and subsequently developed seizures (5/19/2006). Posterior reversible encephalopathy syndrome was diagnosed by MRI findings. Seizures abated following sodium correction, blood pressure control, and phenobarbital administration. In addition, electroencephalography and MRI findings showed improvement.

ISR# 5304334-8, Netherlands, Growth retardation (Consumer report)

A 10 year old male was treated with Gleevec for gastrointestinal stromal tumor. According to his mother, he became grey and suffered from spots, growth deprivation and cold hands and feet. No additional details were provided.

ISR# 5327058-X, France, Growth retardation

A 5 year old male was diagnosed with CML at two years of age. He was treated with Gleevec for 4 to 5 years when a growth retardation (from 2 standard deviations to median curve) was reported. Gleevec was continued.

4.4 Summary of Cases of Gestational Exposure received during the Pediatric Exclusivity Period.

There were three cases of gestational exposure received during the pediatric exclusivity period. One fatal case is described above in Section 4.2.

ISR# 5379658-9, Germany

This is a report of a baby following gestational exposure to Gleevec. The baby's mother was treated with Gleevec since 9/2006. The baby was delivered in week 35 of pregnancy on [redacted] First examination revealed the premature baby was in healthy condition. (No additional details were provided on duration of gestational exposure or specifics on the baby's examination.)

ISR#s 5031806-6 and 5202368-5 (duplicate with additional detail), United Kingdom

This is a report of a female baby following gestational exposure to Gleevec for approximately 25 days. The baby's mother's last menstrual period was 7/4/2005. The mother was treated with Gleevec and G-CSF, which were discontinued upon knowledge of pregnancy (7/29/2005), and interferon alfa-2B and Anti-D immunoglobulin, which were continued during pregnancy. The baby was born [redacted] (38.5 weeks, 2.68kg) and was "normal" apart from a hypoplastic thumb.

4.5 Bone and Metabolic Adverse Events

As noted above in section 4.3, there were two cases of growth retardation reported during the pediatric exclusivity period. In December 2006, a review of bone and mineral metabolism adverse events reported to AERS for all ages was completed. Please see Appendix 1 for this review.

5. Summary/Recommendations

Most of the pediatric cases received during the pediatric exclusivity period described labeled events or expected events due to the child's disease or concomitant medications. Unlabeled events included retroperitoneal fibrosis/hydronephrosis, posterior reversible encephalopathy syndrome, and growth retardation. Attribution of these events to imatinib therapy is difficult to assess due to concomitant use of additional chemotherapeutic agents and ongoing disease. There were also three cases of gestational exposure to imatinib received during the pediatric exclusivity period. One of these cases had a fatal outcome; the baby was born at 30 weeks of pregnancy and died 30 minutes after delivery due to congenital malformation of the heart cavities and connecting structures. The remaining two cases described a baby born in "healthy condition" and a baby born "normal" apart from a hypoplastic thumb. Imatinib is a known animal teratogen (pregnancy category D).

The current labeling for imatinib concerning pediatric patients describes hematologic toxicities and other adverse reactions similar to those seen in adult patients. In addition, women are advised to avoid becoming pregnant while taking imatinib. This review did not identify any adverse reactions that warrant addition to the label. The existing warnings for women to avoid becoming pregnant while taking imatinib are adequate. DDRE continues to routinely monitor reports of adverse events with the use of imatinib in pediatric patients.

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Table 4. Non-fatal pediatric cases received during the pediatric exclusivity period (unlabeled events underlined).

ISR#	Age/ Gender	Source	Outcome	Indication	Event	Time to Onset	Concomitant Medications	Comments
5057157	13/F	UK	HO, OT	Ph+ ALL	<u>Retroperitoneal fibrosis</u> , <u>hydronephrosis</u> , hypertension, pleural effusion, <u>ureteric obstruction</u>	100 days after imatinib initiation	Chemotherapy (agent not specified)	Imatinib discontinued 36 days prior event
5095088, 5073487	9/F	JPN	HO	ALL	Hyponatremia, hypertension, seizures, <u>posterior reversible encephalopathy syndrome</u>	13 days	Vincristine, doxorubicin	EEG/MRI improvement after seizure treatment and imatinib discontinuation
5304334	10/M	NL	OT	GIST	<u>Grey, spots, growth deprivation</u> , cold hands and feet	Not reported		Consumer report, PMH autism
5327058	5/M	FR	DS	CML	<u>Growth retardation</u>	4-5 years	Failed interferon	Growth retardation seen for approx 2 years, Gleevec was ongoing
5065828	6/F	JPN	OT	ALL	<u>ST-T segment abnormality</u>	2 weeks	Daunomycin, doxorubicin	Baseline ECG normal
5066659	15/M	US	HO	CML	Erosive Colitis	Not reported	Methotrexate	PMH of 2 episodes of colitis
5072370	3/M	US	OT	CML	Convulsions	6 months	Occasional ibuprofen	No PMH of convulsions
5164501	6/M	IT	HO	Ph+ ALL	<u>Hallucination</u> , <u>abnormal behavior</u> , <u>stupor</u> , <u>confusional state</u>	42 days	Cyclophosphamide	Patient recovered, imatinib restarted at decreased dose. No psych history.

Table 4 Continued. Non-fatal pediatric cases received during the pediatric exclusivity period (unlabeled events underlined).

ISR#	Age/ Gender	Source	Outcome	Indication	Event	Time to Onset	Concomitant Medications	Comments
5235956	14/M	US	OT	CML	<u>Amnesia</u> , convulsion, headache, <u>muscle twitching</u> , <u>tourette's disorder</u>	363 days	Septra DS	EEG negative, events unchanged at time of report, Gleevec continued
5258416	10/F	US	HO	Ph+ ALL	Fatigue, somnolence, peripheral edema, hypotension	15 days	Ifosfamide, etoposide, strattera, clonidine, protonix, zofran, septra DS	Positive dechallenge
5285112	13/M	UK	HO, OT	Ph+ ALL	<u>EBV infection</u> , hypokalemia, <u>lymphoproliferative d/o</u> , necrosis (lymph node), pyrexia	Not reported	Methotrexate, 6-MP, vincristine	
5289629	13/M	FR	HO	ALL	<u>Blood amylase increased</u> ³	15 days	Foscarnet, omeprazole, pentasa, entocort, nalbuphine, plitican, sporanox, tegeline	Pancreas ultrasound normal structure. Pt not recovered at reporting.
5324906	10/F	COL	DS	CML	<u>Hepatitis A</u> ⁴ , <u>jaundice</u> , transaminases increased	23 months		Dechallenge negative
5347474	13/F	UK	HO	Ph+ ALL	<u>Catheter sepsis</u> , <u>hypomagnesemia</u> , <u>neutropenic sepsis</u>	Not reported	Chemotherapy (agents not specified)	Pt improving at reporting, meds on hold

3 Pancreatitis labeled.

4 Hepatitis labeled.

Appendix 1.

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 18, 2006

FROM: Jennifer Rouine Steele, Pharm.D., Safety Evaluator
 Division of Drug Risk Evaluation

THROUGH: Mark Avigan, M.D., C.M., Director
 Division of Drug Risk Evaluation

TO: Robert Justice, M.D., Director
 Division of Drug Oncology Products

SUBJECT: Postmarketing Safety Review
 Drug: Imatinib Mesylate (Gleevec) NDA# 021588
 Event: Bone and Mineral Metabolism Adverse Events

RCM #: 2006-470

EXECUTIVE SUMMARY

This Division of Drug Oncology Products has requested that DDRE review adverse effects on bone and mineral metabolism associated with imatinib. Specifically, a review of the following events was requested: hypophosphatemia, hypocalcemia, low vitamin D levels, impaired bone mineralization, osteomalacia (rickets), fractures, and other indicators of bone disease. This consult request follows a publication that concluded hypophosphatemia and a series of associated changes in bone and mineral metabolism occurred in some patients receiving imatinib for either chronic myelogenous leukemia or gastrointestinal stromal tumors.³

A search of AERS identified 68 cases that were included in the case series of adverse effects on bone and mineral metabolism associated with imatinib. These cases were divided into four categories including laboratory abnormalities (20), bone anomalies (16), fractures (18), and osteonecrosis (14). In general, characteristics of these cases did not make it possible to establish a consistent pattern, assign causality, or draw conclusions based on the information provided. Many cases had incomplete information (for example, missing information concerning past medical history in many cases and lack of follow-up labs for cases in the lab abnormality section). Falls and other accidents

³Berman E, Nicolaidis M, Maki R et al. Altered Bone and Mineral Metabolism in Patients Receiving Imatinib Mesylate. *NEJM* 354;19:2006-13.

preceded the fracture event in thirteen of eighteen cases, confounding many of the fracture cases. Cases of osteonecrosis were confounded by known risk factors for osteonecrosis including history of leukemia, corticosteroid use and administration of multi-agent chemotherapy. Therefore, interpreting these cases was difficult.

A majority of the cases described use of imatinib for the indication of CML at the approved dosing. Interestingly, the time to onset of event did seem to correlate with the events. For example, lab abnormalities and bone anomalies were reported a median of 51 days and 1.5 years, respectively, from initiation of therapy. This seems to portray a temporal relationship between the events and imatinib therapy, though sufficient data to support this relationship is absent.

Of note is the number of cases of adverse effects on bone and mineral metabolism associated with imatinib as compared to the other tyrosine kinase inhibitors. This could be explained by the fact that imatinib has been marketed the longest of these products. Alternatively, due to the large number of reports in AERS for imatinib, this could be a signal of a true event that is unique to imatinib or one that has yet to be seen with the newer agents (possibly due to smaller number of reports received).

There were six fatal cases. Death was not attributed to imatinib therapy in any of the cases.

Upon completing the review of AERS cases of adverse effects on bone and mineral metabolism associated with imatinib, the data in AERS does not form a clear picture to describe imatinib associated risk or to define the duration, reversibility or clinical significance. Hypophosphatemia, avascular necrosis, and hip osteonecrosis are labeled events for imatinib. Measurements of the effects of imatinib on parathyroid hormone, calcium, and vitamin D pathways as well as bone density and/or bone biopsy studies to characterize the risk and response to imatinib use should be considered, especially in susceptible patients (for example, menopausal woman). Cases of adverse effects on bone and mineral metabolism for the tyrosine kinase inhibitors will continue to be closely monitored.

BACKGROUND

This Division of Drug Oncology Products has requested that DDRE review adverse effects on bone and mineral metabolism associated with imatinib. Specifically, a review of the following events was requested: hypophosphatemia, hypocalcemia, low vitamin D levels, impaired bone mineralization, osteomalacia (rickets), fractures, and other indicators of bone disease. This consult request follows a publication that concluded hypophosphatemia and a series of associated changes in bone and mineral metabolism occurred in some patient receiving imatinib for either chronic myelogenous leukemia or gastrointestinal stromal tumors.⁴

⁴Berman E, Nicolaides M, Maki R et al. Altered Bone and Mineral Metabolism in Patients Receiving Imatinib Mesylate. *NEJM* 354;19:2006-13.

DRUG INFORMATION/LABELING

Imatinib mesylate, a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, was initially approved May 10, 2001 for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Imatinib has since been granted approval for the treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive CML in chronic phase and for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

The product labeling for imatinib includes the following information related to bone and mineral metabolism:

Additional Data From Multiple Clinical Trials

Metabolic and Nutritional: hypophosphatemia (infrequent: estimated 0.1%-1%)

Musculoskeletal: avascular necrosis/hip osteonecrosis (rare: estimated less than 0.1%)

Currently, six tyrosine kinase inhibitors are approved by the FDA. Please see Table 1 below for products, specific characteristics, and relevant labeled adverse events.

Table 1. Tyrosine Kinase Inhibitors			
Drug	Trade Name	Approval Date	Labeling*
Imatinib	Gleevec®	05/10/2001	Hypophosphatemia, avascular necrosis/hip osteonecrosis
Dasatinib	Sprycel™	06/28/2006	Hypocalcemia, hypophosphatemia
Erlotinib	Tarceva®	11/18/2004	None
Gefitinib	Iressa®	05/05/2003	None
Sorafenib	Nexavar®	12/20/2005	Hypophosphatemia
Sunitinib	Sutent®	01/26/2006	Hypophosphatemia, bone abnormalities in developing rats

*Labeling pertaining to bone and mineral metabolism disorders.

SEARCH STRATEGY AND RESULTS

A search of the AERS database was performed October 16, 2006 using the active ingredient imatinib mesylate and the trade name Gleevec and the following MedDRA terms:

- Bone, calcium, magnesium and phosphorus metabolism disorders (HLGT)
- Fractures (HLGT)
- Bone disorders (HLT)
- Bone metabolism disorders (HLT)
- Metabolic bone disorders (HLT)
- Vitamin analyses (HLT)

Of the 3,936 cases associated with imatinib in AERS, this search strategy yielded 84 unduplicated cases. Sixty-eight of these cases were included in the case series. Sixteen cases were excluded as they reported hypercalcemia (5), hypomagnesemia (5), an adverse event occurring prior to initiation of imatinib (3), jaw swelling following a root canal (1), and blood folate decreased (1). One additional case was excluded as the patient did not receive imatinib.

Additional searches of the AERS database were done to determine the number of specific preferred terms associated with the approved tyrosine kinase inhibitors. Please see the Tables 2, 3, and 4 below for the number of AERS reports and selected outcomes associated with the approved tyrosine kinase inhibitors and the preferred terms osteonecrosis, hypophosphataemia, and hypocalcemia. Searches were performed for the preferred terms vitamin D decreased and vitamin D deficiency for the approved tyrosine kinase inhibitors which yielded zero cases for all products.⁵

Table 2. Osteonecrosis (PT) – AERS Crude Counts and Outcomes†				
Drug	Total AERS Reports	Death	Serious	Hospitalized
Imatinib	18	0	18	5
Dasatinib	1	0	1	1
Erlotinib	0	-	-	-
Gefitinib	1	0	1	0
Sorafenib	2	0	2	2
Sunitinib	2	1	2	0

Table 3. Hypophosphataemia (PT) – AERS Crude Counts and Outcomes†				
Drug	Total AERS Reports	Death	Serious	Hospitalized
Imatinib	7	0	6	3
Dasatinib	0	-	-	-
Erlotinib	2	0	1	0
Gefitinib	2	0	2	2
Sorafenib	2	0	2	2
Sunitinib	0	-	-	-

Table 4. Hypocalcemia (PT) – AERS Crude Counts and Outcomes†				
Drug	Total AERS Reports	Death	Serious	Hospitalized
Imatinib	17	2	17	4
Dasatinib	0	-	-	-
Erlotinib	2	0	2	1
Gefitinib	7	0	6	5
Sorafenib	7	0	7	7
Sunitinib	5	1	5	5

⁵ AERS search date November 9, 2006.

†Crude counts, may include duplicates; US and foreign reports since beginning of marketing.

SUMMARY OF CASES

Table 5. Characteristics of All Cases (n=68)	
Age (years) (n=59)	Range 4 to 90 Median 58
Gender	Female 31 Male 32
Indication	CML 40 GIST 6 Glioblastoma multiforme 3 Lung cancer 3 ALL 2 Thyroid cancer 2 Prostate cancer 1 Oral cancer 1 Mastocytosis 1 Kaposi's sarcoma 1 Pancreatic cancer 1
Outcome	Death 6 Hospitalized 32 Disabled 6 Life-threatening 3 Other 38
Concomitant Medications (n=13)	Hydroxyurea 2 Docetaxel 2 Vincristine 2 Temozolomide 2 Prednisolone 2 Dexamethasone 1 Gemcitabine 1 Cyclophosphamide 1 Doxorubicin 1 Cisplatin 1 Bicalutamide 1 Chemotherapeutic (not specified) 1 Corticosteroid (not specified) 1
Report Source	USA 21 Foreign 47
Report Type	15-day Expedited 62 Direct 3 Periodic 3

Laboratory Abnormalities

Twenty cases described laboratory abnormalities including hypocalcemia (15), hypophosphatemia (7), and decreased vitamin D (1)⁶. Additionally, there was one case each of a bone disorder (described with decreased vitamin D), stress fracture (described with hypocalcemia and hypophosphatemia), and osteoporosis (described with hypocalcemia). Median patient age was 57.5 years (range 4 to 78 years). There were 13 male and 6 female cases. Time to onset of event was a median of 51 days (range 6 days to 4.4 years) from initiation of imatinib therapy. Indication for use of imatinib included CML (8), lung cancer (2), thyroid cancer (2), GIST (1), Kaposi's sarcoma (1), glioblastoma multiforme (1), pancreatic cancer (1), and ALL (1). Median dose of imatinib was 400mg per day (range 200mg to 1200 mg per day).

Representative Case

ISR# 4170530-9 (US, 15-day)

A 68 year old female with bronchioloalveolar carcinoma was enrolled in a phase I pharmacokinetic study of daily imatinib in combination with every three week docetaxel. The patient had a history of a thyroidectomy (1968), mastectomy, and myocardial infarction with paroxysmal atrial fibrillation. Concomitant medications included Synthroid, Rocaltrol, and Oscal. Baseline serum calcium was 7.6 (8.4-10.2). Fifteen days after initiation of imatinib 400mg daily, the patient was hospitalized due to hypocalcemia (serum calcium 5.6) and febrile neutropenia (although patient was afebrile upon admission to the hospital). Imatinib was discontinued and the patient was treated with IV calcium gluconate. The day following admission, her ionized calcium was 0.81 (normal not specified). She was discharged four days later with a serum calcium of 6.3 and an ionized calcium of 0.95. Two weeks later, her serum calcium was 8.8, within the normal range.

Bone Anomalies

Sixteen cases described bone anomalies including osteoporosis (5), bone disorder (4), osteolysis (3), spinal disorder (3), bone density decreased (2), extraskeletal ossification (1), bone erosion (1), delayed osteogenesis (1), and bone lesion (1).⁴ Median patient age was 52 years (range 6 to 90 years). There were 9 female and 7 male cases. Time to onset of event was a median of 1.5 years (range 2 months to 'several' years) from initiation of imatinib therapy. Indication for use of imatinib included CML (10), GIST (1), prostate cancer (1), oral cancer (1), mastocytosis (1), and glioblastoma multiforme (1). Median dose of imatinib was 400mg per day (range 100mg to 800mg per day). Concomitant medications were not specified in ten cases. There was one case each of concomitant use of pamidronate and corticosteroids.

⁶ Each case may contain more than one event.

The following information pertains to the five cases of osteoporosis:

- One case was diagnosed by bone density test (please see Representative Case below).
- Two cases were reported from the same physician who described abnormal x-rays after several years of imatinib therapy which was possibly osteoporosis in each case.
- The fourth case described a patient with decreased bone density 7 months after initiation of imatinib for mastocytosis. The patient's relevant medical history included the use of corticosteroids. The reporting physician considered the event unlikely and not related to imatinib therapy and noted this was a frequent symptom of patients with mastocytosis.
- The fifth case was a consumer report of degeneration of the spine and osteoporosis about 2 months after starting imatinib.

Representative Case

ISR# 5048072-8 (US, 15-day)

A 50 year old male was receiving imatinib 800mg daily for CML. Almost three years after initiation of therapy, the physician ordered a bone density study after reading a medical journal report of hypophosphatemia due to imatinib although the patient had no known risk factors for osteoporosis and was asymptomatic. The patient had a T score of -3.44, Z score of -2.24 and was started on alendronate.

Fractures

Eighteen cases described bone fractures including fractures of the vertebra (3), rib (2), femur (2), hip (1), foot (1), jaw (1), sacrum (1), pelvis (1), thumb (1), dens (1), wrist (1), and shoulder (1). Of two additional cases, one described a cervical vertebral fracture and an arm fracture following a fall and the other did not specify the site of the fracture. Median patient age was 65 years (range 21 to 82 years). There were 10 female and 8 male cases. Time to onset of event was a median of 13 months (range 1 month to 3 years) from initiation of imatinib therapy. Indication for use of imatinib included CML (13), GIST (1), glioblastoma multiforme (1), and lung cancer (1). Median dose of imatinib was 400mg per day (range 200mg to 1000mg per day). The fracture event followed a fall in eleven cases. Additionally, there was one case of a fracture following a fight (jaw fracture) and one case following an electrocution.

Osteonecrosis

Fourteen cases described osteonecrosis including osteonecrosis of the femoral head (3), hip (3), shoulder (2), ankle (2), external auditory canal bone (1), arm (1), humerus head (1), femur (1), knee (1), and tibia (1).⁷ Median patient age was 49 years (range 17 to 73

⁷ Each case may contain more than one event.

years). There were 6 female and 4 male cases. Time to onset of event was a median of 1.8 years (range 4 weeks to 2 years 3 months) from initiation of imatinib therapy. Indication for use of imatinib included CML (9), GIST (3), and ALL (1). Median dose of imatinib was 400mg per day (range 300mg to 600mg per day). The treatment for osteonecrosis was specified in only two cases; one patient received tramadol and meloxicam and the other patient had a hip replacement secondary to osteonecrosis (See Representative Case below). One case documented concomitant use of a corticosteroid, a known risk factor for osteonecrosis.

Representative Case

ISR #4255220-6 (US, 15-day)

A 45 year old female was receiving imatinib since March 2001 for CML. Prior to imatinib therapy she received pegylated interferon from 1999 to October 2000. In [redacted], an MRI revealed avascular necrosis (AVN) in both hips. In [redacted], MRI revealed AVN of the right ankle and in [redacted] an MRI revealed AVN of the right shoulder. In [redacted], the patient underwent left hip replacement secondary to AVN. The patient was maintained on imatinib 300 to 400mg daily throughout these events.

Fatal Cases

Six cases had a fatal outcome. Indication for use of imatinib included CML (3), GIST (2), and prostate cancer (1). Median patient age was 73 years (range 50 to 90 years). There were 4 male and 2 female cases. The median duration of imatinib therapy was 4.5 months (range 15 days to 7 months). Death occurred a median of 15.5 days after discontinuation of imatinib therapy (range 3 to 83 days). The cause of death for these cases was reported as follows:

- COPD
- Aspiration pneumonia and SIRS
- Sepsis
- Multi-organ failure and DIC
- Consumer report of “fatal drug reaction from a drug delivered via a catheter”
- Patient transferred to hospice, cause of death not specified

DISCUSSION

The cases included in the case series did not provide a succinct picture of adverse effects on bone and mineral metabolism associated with imatinib. Characteristics of these cases did not make it possible to establish a consistent pattern, assign causality, or draw conclusions based on the information provided. Many cases had incomplete information (for example, missing information concerning past medical history in many cases and lack of follow-up labs for cases in the lab abnormality section). Falls and other accidents preceded the fracture event in thirteen of eighteen cases, confounding many of the fracture cases. Cases of osteonecrosis were confounded by known risk factors for

osteonecrosis including history of leukemia, corticosteroid use and administration of multi-agent chemotherapy. Therefore, interpreting these cases was difficult.

A majority of the cases described use of imatinib for the indication of CML at the approved dosing. Interestingly, the time to onset of event did seem to correlate with the events. For example, lab abnormalities and bone anomalies were reported a median of 51 days and 1.5 years, respectively, from initiation of therapy. This seems to portray a temporal relationship between the events and imatinib therapy, though sufficient data to support this relationship is absent.

Of note is the number of cases of adverse effects on bone and mineral metabolism associated with imatinib as compared to the other tyrosine kinase inhibitors. This could be explained by the fact that imatinib has been marketed the longest of these products. Alternatively, due to the large number of reports in AERS for imatinib, this could be a signal of a true event that is unique to imatinib or one that has yet to be seen with the newer agents (possibly due to smaller number of reports received).

Concerning the six fatal cases, death was not attributed to imatinib therapy in any of the cases.

CONCLUSION

A review of AERS cases of adverse effects on bone and mineral metabolism associated with imatinib was performed. Hypophosphatemia, avascular necrosis, and hip osteonecrosis are labeled events for imatinib. The data in AERS does not form a clear picture to describe imatinib associated risk or to define the duration, reversibility or clinical significance. Measurements of the effects of imatinib on parathyroid hormone, calcium, and vitamin D pathways as well as bone density and/or bone biopsy studies to characterize the risk and response to imatinib use should be considered, especially in susceptible patients (for example, menopausal woman). Cases of adverse effects on bone and mineral metabolism for the tyrosine kinase inhibitors will continue to be closely monitored.

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