Dasatinib for Newly Diagnosed Adults with Ph (+) Chronic Myelogenous Leukemia in Chronic Phase and Safety Update
National Drug Monograph Addendum
November, May 2012
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum provides information on the use of dasatinib for use in newly diagnosed adults with Ph (+) Chronic Myelogenous Leukemia (CML) in chronic phase as well as information concerning the Pulmonary Arterial Hypertension warning added to the prescribing information. The original drug monograph can be found at:


Introduction
Dasatinib receiving initial FDA approval in 2006 for the treatment of adults with chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. FDA approval also included adults with Ph+ Acute Lymphoblastic Leukemia (ALL) with resistance or intolerance to prior therapy. The use of dasatinib for newly diagnosed adults with Ph+ CML in chronic phase became an FDA-approved indication in October, 2010. This addendum will summarize the data for use in newly diagnosed CML patients in chronic phase as well as the data that led to the inclusion of Pulmonary Arterial Hypertension (PAH) to Warnings and Precautions within the prescribing information. The PAH warning was added in October, 2011.

Dosing and Administration
The recommended dose of dasatinib for chronic phase CML is 100 mg orally, once daily. For accelerated phase CML, myeloid or lymphoid blast phase CML or Ph+ ALL, the recommended dose is 140 mg orally, once daily. Doses are to be given by mouth, with or without a meal. Tablets should not be crushed or cut.

Change in Efficacy Measures
The dasatinib monograph describes efficacy measures that were pertinent to monitoring TKI therapy at that time. Cytogenetic and hematologic responses were the primary endpoints used to evaluate efficacy. With the use of fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR) techniques, response can be evaluated on a molecular level. Major molecular response (MMR) is added to the list of efficacy measures and is defined as a BCR-ABL transcript level of \(< 0.1\%\) on the International Scale, which corresponds to a 3 log reduction in transcript level from the standard baseline level.

The depth of MMR, as well as the time to achieve MMR may correlate with improved outcomes. Researchers are also focusing on the MMR depth to assist with defining the point at which TKI therapy may possibly be discontinued. Definitions to further characterize molecular response have been recently published.

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Published management guidelines from the European LeukemiaNet define overall response to imatinib therapy.\(^3\)

<table>
<thead>
<tr>
<th>Evaluation time</th>
<th>Optimal response</th>
<th>Suboptimal response</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>CHR and at least minor CyR (Ph+ ≤ 65%)</td>
<td>No CyR (Ph+ &gt; 95%)</td>
<td>Less than CHR</td>
</tr>
<tr>
<td>6 months</td>
<td>At least partial CyR (Ph+ ≤ 35%)</td>
<td>Less than partial CyR (Ph+ &gt; 35%)</td>
<td>No CyR (Ph+ &gt; 95%)</td>
</tr>
<tr>
<td>12 months</td>
<td>CCyR</td>
<td>Partial CyR (Ph+ 1-35%)</td>
<td>Less than partial CyR (Ph+ &gt; 35%)</td>
</tr>
<tr>
<td>18 months</td>
<td>MMR</td>
<td>Loss of MMR; mutations change</td>
<td>Loss of CHR, CCyR, mutations, clonal progression</td>
</tr>
<tr>
<td>Any time during treatment</td>
<td>Stable or improving MMR</td>
<td></td>
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</table>

CHR = complete hematologic response defined as WBC < 10 x 10^9/L, basophils < 5%, no myelocytes, promyelocytes, myeloblasts in the differential, platelet count < 450 x 10^9/L, nonpalpable spleen; CyR = cytogenetic response, which requires the karyotyping of at least 20 metaphase cells from the bone marrow aspirate; CCyR = complete cytogenetic response defined as no Ph+ cells in metaphase; PCyR = partial cytogenetic response defined as 1-35% Ph+ metaphases; MCyR = major cytogenetic response defined as CCyR + PCyR; mCyR = minor cytogenetic response defined as 36-65% Ph+ metaphases; minCyR = minimal cytogenetic response defined as 66-95% Ph+ metaphases; noCyR = no cytogenetic response defined as > 95% Ph+ metaphases; Ph+ = Philadelphia chromosome positive; MMR = molecular response, defined as ratio of BCR-ABL1 to ABL1 or other housekeeping genes of < 0.1 % on the international scale

**Newly Diagnosed Ph+ CML in Chronic Phase** \(^6\), \(^7\), \(^8\), \(^9\)

The phase III results from DASISION published by Kantarjian et al. provides comparative data between dasatinib and imatinib among newly diagnosed patients with Ph+ CML in chronic phase. Their initial report, published after 12 months of follow-up had been completed, indicates that patients receiving dasatinib achieved significantly higher rates of CCyR and MMR.\(^6\) A follow-up report at 24 months notes that although the CCyR no longer had statistical significance, the MMR maintained a statistical difference.\(^7\) These data, highlighting the faster, deeper responses with dasatinib compared to imatinib, led to accelerated approval by the FDA for the treatment of newly diagnosed CML.

For comparison, the 60-month follow-up of IRIS (International Randomized study of Interferon and STI571) show that the responses noted with imatinib are durable.\(^8\) The annual rate of progression to accelerated phase (AP) or blast crisis (BC) was 0.6 percent in the fifth year of therapy. Those who achieved a CCyR by 12 months had better overall survival compared to those who did not obtain at least a major cytogenetic response. Patients with a CCyR and at least a 3 log reduction of BCR-ABL transcripts at 12 months did not progress to either AP or BC at 60 months. Of note, there is criticism that the 5-year results of IRIS may have been over-estimated, citing the lack of an intent-to-treat analysis. Some patients were censored prior to month 48 for reasons other than disease progression. These reasons included: unsatisfactory response (11%), withdrawal of consent (5%) and adverse events (4%). Including those censored patients as treatment failures, lowers the response (event-free survival) from 83% to 62.7%.\(^13\), \(^14\)

An 8-year follow up report of IRIS indicates that the estimated event-free survival was 81% and freedom from progression to AP/BC was 92%. The annual rate of progression to AP/BC at year 8 was 0.4%. The rate of MMR increased from 24% at 6 months and 39% at 12 months to a best observed rate of 86%. Patients with a minor CyR (> 0-65% Ph+ metaphases) at 3 months; partial CyR (> 0-35% Ph+ metaphases) at 6 and 12 months; and CCyR at 18 months obtained a stable CCyR over the time course.\(^9\)

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It is hypothesized that if patients can achieve the goal of CCyR sooner, then perhaps long-term outcomes can be improved. The second-generation TKI’s have shown that achieving a CCyR sooner is possible. Although it is unclear that a faster, deeper response correlates with improved long-term outcomes, as our length of follow-up with the second-generation agents is limited.

Safety results from DASISION indicate that dasatinib and imatinib share differing adverse event profiles. Bone marrow suppression, specifically neutropenia and thrombocytopenia, were comparable between dasatinib and imatinib. Differences lie in their non-hematologic profiles. Imatinib showed higher rates of all grades of fluid retention, nausea and myalgia, while dasatinib had higher rates of pleural effusion. The rate of diarrhea was comparable between both agents, as was muscle pain.

Refer to Table 1 for detailed trial results.

**Warning and Precautions: Pulmonary Arterial Hypertension**

Post-Marketing Surveillance reports identified an increase in the risk of Pulmonary Arterial Hypertension (PAH) among patients receiving dasatinib. This warning was added to the manufacturer’s label in October, 2011. Prescribing information states that the risk of developing PAH may occur any time after dasatinib therapy initiation, including after more than one year of treatment. Symptoms of PAH may include shortness of breath, fatigue, hypoxia and fluid retention. Labeling also notes that PAH may be reversible after discontinuation of dasatinib and recommends that patients be evaluated for cardiopulmonary disease prior to initiating therapy and while therapy is ongoing. Dasatinib should be discontinued permanently if the diagnosis of PAH is confirmed.

The French pulmonary hypertension (PH) registry reports that nine incident cases of PH were described from the time of dasatinib approval (November, 2006) to September, 2010. Eight of these patients were female. The time between the initiation of dasatinib and diagnosis of PH was a median of 34 months (range, 8-48 months) indicating that this was a late complication of therapy. All patients were receiving dasatinib in the second-line setting.

Other reports of dasatinib-induced PAH have been published in the literature. In all cases, these patients were receiving dasatinib in the second-line setting. Some patients improved symptomatically with discontinuation of dasatinib alone while others required the addition of vasodilator therapy for further improvement. No patients were re-challenged with dasatinib. Those changed to an alternative tyrosine kinase inhibitor showed no signs of PAH recurrence.

The rapid relief of symptoms and hemodynamic improvements after withdrawal of dasatinib are consistent with a reversible component. Some reports have noted complete reversibility of PH, but have not performed invasive hemodynamic evaluations to confirm. Absence of complete resolution in some cases suggests that perhaps some degree of pulmonary vasculature remodeling may take place.

There have been no reports of PAH with imatinib or nilotinib. Interestingly, imatinib is being researched as a potential treatment for PAH. Although results have not been released, the Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) has been completed. Dasatinib is comparable to imatinib with its similar effects on c-kit and Platelet Derived Growth Factor Receptor (PDGFR). Dasatinib also inhibits the SRC family of kinases. Src kinases play a key functional role in essential signaling pathways that are involved in cell proliferation, vasodilation and vasoconstriction. Whether this difference in tyrosine kinase activity is causally related to PH is unclear, but provides a theoretical basis.

Longer term follow-up is needed to characterize the natural history and outcomes of dasatinib-induced PH.

In the case reports of PAH to date, dasatinib had been given as a second-line therapy. As the potential for increased utilization of dasatinib follows the FDA approval as a first-line therapy, a subsequent increase in number of PAH cases may result. Patient evaluation prior to the initiation of dasatinib and appropriate monitoring throughout therapy will be essential for veteran safety. Those experiencing symptoms consistent with PAH, should discontinue dasatinib therapy while a PAH diagnosis is in process of work-up. Subsequent reporting of incidents to VA MedSafe will be important to further characterize this effect among the veteran population.
Conclusions

Dasatinib, a second-generation tyrosine kinase inhibitor, initially entered the U.S. market as a second-line therapy in CML for those with intolerance or resistance to imatinib therapy. The most recent FDA-approval places dasatinib as a first-line therapy for chronic phase disease. Dasatinib is considered to be a more potent TKI than imatinib. It shares mechanistic similarities with imatinib, such as inhibition of c-kit and PDGFR, but also a unique role of inhibiting Scr kinases. These differences in action may provide the rationale for the differing adverse effect profiles between these drugs.

As previously noted from IRIS, those patients who achieved a CCyR by 12 months had better overall survival compared to those who did not obtain at least a major cytogenetic response. DAISISION has shown that with dasatinib, patients can achieve the goal of CCyR sooner than with imatinib. It is unclear that a faster, deeper response correlates with improved long-term outcomes, as our length of follow-up with the dasatinib is limited, but growing.

The adverse effect profile of dasatinib is different from the other TKI’s. Careful selection of patients, ruling out any preexisting cardiopulmonary disease, is necessary given the reports and risk of PAH. Patients should be monitored for any signs and symptoms of PAH during treatment as well. Those experiencing symptoms consistent with PAH, should discontinue dasatinib therapy while a PAH diagnosis is in process of work-up. Subsequent reporting of incidents to VAMedSafe will be important to further characterize this effect among the veteran population.
### Table 1. Summary of Clinical Trials Investigating Use of Dasatinib for Newly Diagnosed Adult Patients with Ph+ CML in Chronic Phase

<table>
<thead>
<tr>
<th>Citation</th>
<th>Design</th>
<th>Analysis type</th>
<th>Setting</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Patient Population Profile</th>
<th>Efficacy Results</th>
<th>Safety Results</th>
<th>Critique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantarjian (2010)</td>
<td>DASISION</td>
<td>Open-label, multinational, randomized, phase 3 trial</td>
<td>Inclusion: Adults, Ph+ CML, Chronic phase, no prior treatment except anagrelide or hydroxyurea, ECOG PS 0-2, adequate hepatic &amp; renal function (defined as max Tbili 2x ULN, max AST/ALT 2.5x ULN, Max SCR 3x ULN)</td>
<td>1:1 ratio N= 519 Dasatinib 100mg orally once daily or Imatinib 400mg orally once daily</td>
<td>Primary endpoint: CCR @ 12 mos: 77 vs. 66%; P=0.007 Grade 3 / 4 Neutropenia</td>
<td>N= 519 Dasatinib 259; Imatinib 260</td>
<td>CCR @ 12 mos: 77 vs. 66%; P=0.007 Grade 3 / 4 Neutropenia</td>
<td>MMR @ 12 mos: 46 vs. 28% P&lt;0.0001 All grades Fluid retention 19 vs. 42% Pleural effusion 10 vs. 0% Diarrhea 17 vs. 17% Nausea 8 vs. 20% Muscle pain 11 vs. 14% Rash 11 vs. 17%</td>
<td>Dasatinib was associated with significantly higher and faster rates of CCR and MMR. Longer follow-up may show that dasatinib improves long-term outcomes for newly diagnosed patients.</td>
</tr>
<tr>
<td>Kantarjian (2012)</td>
<td>DASISION</td>
<td>Open-label, multinational, randomized, phase 3 trial</td>
<td>Exclusion: Women breast feeding, pregnant or with potential and did not have neg pregnancy test, serious uncontrolled medical disorders or active infection, prior chemo for SCT, pleural effusions</td>
<td>1:1 ratio N= 519 Dasatinib 100mg orally once daily or Imatinib 400mg orally once daily</td>
<td>Secondary: MMR³ Duration: Treatment continued until disease progression or treatment toxicity</td>
<td>N= 519 Dasatinib 259; Imatinib 260</td>
<td>CCR rate: 3, 6 and 9 months: 76, 73 and 78% vs. 71, 59 and 67% All grades Fluid retention 19 vs. 42% Pleural effusion 10 vs. 0% Diarrhea 17 vs. 17% Nausea 8 vs. 20% Muscle pain 11 vs. 14% Rash 11 vs. 17%</td>
<td>MMR rate: 64 vs. 46% P&lt;0.0001 Rates of DC 5 vs. 4%</td>
<td>Dasatinib enables patients to achieve faster and deeper responses.</td>
</tr>
</tbody>
</table>

#### Notes

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<th>Efficacy Results</th>
<th>Safety Results</th>
<th>Author’s conclusions (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>months</td>
<td></td>
<td></td>
<td>59 vs. 43% Dose reduction: 28 vs. 15% Dose escalation: 7 vs. 20%</td>
<td>4.5-log reduction in BCR-ABL transcript level: 17 vs 8% P=0.002</td>
<td>Non-heme AEs Fluid retention 25 vs. 42% Superficial edema 11 vs. 36% Pleural effusion 14 vs. 0% Myalgia 22 vs. 39% Nausea 10 vs. 23%</td>
<td>compared to imatinib.</td>
</tr>
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$^a$CCR = Complete Cytogenetic Response defined as the absence of Ph+ metaphases within at least 20 cells in metaphase per BM sample, documented on 2 consecutive assessments at least 28 days apart.

$^b$MMR = Major Molecular Response, defined as BCR-ABL transcript level ≤ 0.1% on the International Scale; this corresponds to at least a 3 log reduction from standardized baseline level.

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References: