Medical Services Advisory Committee

Public Summary Document

Application No. 1125 – Molecular testing for myeloproliferative disease

Sponsor: **Pathology Services Table Committee, Department of Health and Ageing**

Date of MSAC consideration: **47th MSAC meeting, 4 December 2009**

Part B – Systemic mast cell disease, hypereosinophilic syndrome and chronic eosinophilic leukaemia

1. Purpose of Application

An application from the Pathology Services Table Committee, Department of Health and Ageing was made to MSAC to conduct a systematic review of the literature and an economic evaluation of molecular testing in myeloproliferative disorders.

2. Background

Systemic mast cell disease

Molecular testing in patients with systemic mast cell disease (SMCD) enables the detection of relevant mutations known to occur in patients with this disease. Specific mutations include the *KIT*D816V mutation and, although other *KIT* mutations are known to occur in SMCD, the D816V is the most prevalent. In a small number of patients with SMCD who also present with eosinophilia, the presence of the *FIP1L1-PDGFRA* rearrangement is found. The small subset of patients with aggressive systemic mastocytosis who have the oncogenic *FIP1L1-PDGFRA* rearrangement do not harbour the *KIT*D816V mutation (ie the mutations are mutually exclusive). Patients with aggressive SM driven by the *KIT*D816V mutation are not sensitive to imatinib mesylate. In contrast, patients with the *FIP1L1-PDGFRA* rearrangement (and by definition not the *KIT*D816V mutation) and are sensitive to imatinib.

Molecular testing alone is not sufficient for the diagnosis of SMCD; rather, it is used in addition to conventional testing (including bone marrow biopsy, serum tryptase levels and flow cytometry). The methodology required to determine the presence of a relevant genetic alteration is mostly dependent on the type of mutation being considered. For *KIT* mutations, qualitative polymerase chain reaction (PCR)-based methods are adequate to reliably detect the presence of a mutation. Due to the low number of mast cells in the peripheral circulation, it is appropriate to conduct this analysis on genetic material obtained from bone marrow biopsy.

The detection of the *FIP1L1-PDGFRA* fusion gene or other genetic rearrangements requires more complex methods such as reverse transcriptase PCR or fluorescent in-situ hybridisation to detect a deletion of genetic material that includes the *CHIC2* gene, and results in the fusion of the *FIP1L1* and *PDGFRA* genes.

The comparator test strategy, against which molecular testing for the investigation of suspected SMCD is assessed, is all available clinical and laboratory information, which can include bone marrow biopsy, serum tryptase levels and flow cytometry.

Hypereosinophilic syndrome and chronic eosinophilic leukaemia

Evidence of clonal eosinophilia, either the presence of a relevant genetic alteration or otherwise, enables a diagnosis of chronic eosinophilic leukaemia (CEL); the absence of such evidence allows a diagnosis of hypereosinophilic syndrome (HES). Molecular testing in patients with persistent eosinophilia can provide evidence of a clonal eosinophilic disorder. In addition, the presence of the *FIP1L1-PDGFRA* or other *PDGFR* rearrangements can predict a clinical response to imatinib mesylate.

Patients with HES associated with abnormal lymphocytes would undergo further molecular analysis of the FGFR1 gene, and the presence of this gene would exclude a diagnosis of T-cell associated HES.

As is the case for SMCD, molecular testing for these disorders is insufficient for a diagnosis of HES or CEL, and would be additional to present procedures (molecular analysis, determination of serum tryptase levels and echocardiography) but has the potential to improve diagnosis and direct therapy with imatinib.

3. Clinical Need

There are no readily available data regarding the clinical need for molecular testing in the diagnosis of SMCD in Australia. Expert opinion suggests that this disorder is very rare in clinical practice and that fewer than 150 people would be investigated per year for SMCD. The natural history of the subgroup of individuals with the FIP1L1-PDGFRA rearrangement with standard therapy is unknown however case series show that some patients achieve complete haematological remissions with imatinib. Imatinib is on the PBS for this condition and without molecular testing the subgroup of individuals who may benefit from this drug cannot be identified.

Similarly, there is an absence of data regarding the clinical need and burden of disease of HES or CEL in Australia. The expert opinion of the Advisory Panel indicated that these disorders were likely to be rarer than SMCD in clinical practice and estimated that up to 50 investigations for HES or CEL would be required per year in Australia. It was noted that treatment with imatinib is subsidised on the PBS for patients with the FIP1L1-PDGFRA fusion gene and HES or CEL and by inference the drug must have been considered cost effective in this subgroup of HES/CEL patients.

4. Comparator

The comparator is conventional testing alone, which includes all available clinical and laboratory information required to make a diagnosis, and it is likely that imatinib treatment will result in better outcomes in selected patients with SMCD, HES or CEL.

5. Safety

MSAC found that the overall risk associated with sample collection was considered small. As patients would provide a peripheral blood sample and bone marrow biopsy regardless of the testing strategy they underwent, genetic material could be obtained from these without the need for further sample collection.

6. Clinical effectiveness

Overall, the linked evidence approach consisted of low-level evidence that was often limited by small patient numbers. With further evidence unlikely to become available due to the very low prevalence of SMCD, it is expected that investigation of patients with SMCD with the addition of molecular analysis is likely to be at least as effective as the comparator test strategy (without molecular analysis). In patients with suspected SMCD associated with a persistent eosinophilia,

the addition of molecular analysis to the test strategy is likely to be more effective than the comparator in predicting the likelihood of response to imatinib.

No studies were available that considered the use of molecular analysis of the *FGFR1* gene in the diagnosis of T-cell-associated HES.

Direct evidence of effectiveness of molecular testing in the diagnosis of HES and CEL was limited to a small case series that provided weak evidence of a benefit to patients diagnosed with CEL with the addition of molecular analysis and, subsequently, receiving treatment with imatinib mesylate. However, no comparative evidence was available that compared the health consequences of diagnosis with molecular analysis to diagnosis without. Consequently, a linked evidence approach was undertaken.

Only low-level evidence was available to assess test accuracy and results were inconsistent. In the absence of comparative data, it is not possible to establish the accuracy of diagnosis with molecular analysis; however, as it would be used in addition to the comparator, it is likely that it would be at least as accurate as diagnosis without molecular analysis.

MSAC noted that molecular testing is a requirement for prescribing the drug imatinib mesylate which can lead to some patients becoming disease free. This may lead to an increase usage and subsequent cost to the Pharmaceutical Benefits Scheme (PBS). It was also noted that molecular testing could assist with targeting chemotherapy.

7. Cost-effectiveness

In the absence of suitable data and some uncertainty regarding the extent of any net benefit of molecular analysis in the diagnosis of SMCD, a cost-effectiveness analysis was not conducted. Rather, a financial analysis of the cost implications associated with the addition of molecular analysis to the diagnostic strategy for this population was undertaken. The incremental cost per patient having this molecular test is $323. No cost-offsets arise from reductions in the use of other tests because, as indicated above, this molecular test would be used in addition to other diagnostic tests already in use. Of the 134 patients expected to be tested each year, an additional 4 patients will likely be identified as benefiting from imatinib treatment at a cost of $47,672 per year of treatment.

The absence of comparative evidence evaluating the effectiveness of molecular analysis in the diagnosis of HES and CEL prevented a formal economic evaluation being conducted. Again, a financial analysis of the cost implications associated with the addition of molecular analysis to the diagnostic strategy for this population was undertaken. It is anticipated that 50 patients will be tested each year at an incremental cost of $233 per year. No cost-offsets arise from reductions in the use of other tests because, as with SMCD, this molecular test would be used in addition to other diagnostic tests already in use. Due to the complete absence of data regarding the use of *FGFR1* analysis in the diagnosis of HES, testing for this rearrangement was not considered in the financial analysis.

8. Financial/budgetary impacts

The direct costs of the addition of molecular analysis in the diagnosis of HES and CEL were considered with respect to the Australian healthcare system overall and to the Commonwealth as a consequence of the Medicare rebate for private patients.

For SMCD with an expected 134 investigations required per year, it is estimated that 80% of investigations would be eligible for Medicare reimbursement. Consequently, the cost implications to the MBS of the addition of molecular analysis of both *KIT* and *FIP1L1-PDGFRA* to the diagnostic strategy would be $22,000 per year.

For HES/CEL, the expert opinion of the Advisory Panel is that up to 50 investigations of suspected HES or CEL will be required per year, of which 80% will be eligible for Medicare reimbursement. The cost to the MBS as a consequence of the Medicare rebate would be $7,000 per year.

MSAC noted that, because of the small numbers of patients likely to be tested for SMCD and HES/CEL each year, and the relatively low unit costs of the tests ($90-$233), the financial impact on the MBS is not likely to be large, but that a major cost flow-on might arise due to the increased use of imatinib in patients with SMCD. For this indication, the cost to the Australian healthcare system overall, including the cost of treatment with imatinib mesylate in patients with SMCD associated with eosinophilia and the *FIP1L1-PDGFRA* rearrangement, would result in an additional cost of $234,000 per year, of which $43,282 is for the molecular analysis. The majority of the overall cost is due to the cost of imatinib mesylate therapy ($190,688). By comparison, the addition of molecular analysis of suspected HES or CEL would result in an additional cost of tests of $11,800 to the Australian healthcare system per year.

9. Summary of consideration and rationale for MSAC's advice

MSAC noted that molecular testing for *FIP1L1-PDGFRA* rearrangement in SMCD, HES and CEL would allow the identification of patients who may respond to imatinib. It was also noted that imatinib is available on the PBS for this subgroup of patients.

MSAC also noted that the cost of molecular testing for these myeloproliferative disorders would be relatively low given the small numbers of patients and low cost of the tests.

MSAC voted to advise the Minister that public funding should be supported for the molecular test for the FIP1L1-PDGFRA rearrangement but not for *KIT* mutations.

10. MSAC's advice to the Minister

Based on the clinical need in a small group of patients with serious disease, and the likely clinical effectiveness in terms of determining sensitivity to imatinib treatment, MSAC supports public funding of molecular testing to assist with the diagnosis and management of SMCD, HES and CEL by molecular testing for the FIPIL1-PDGFRA fusion gene.

MSAC does not support public funding of the molecular tests for KIT mutations as the KIT mutation and the FIP1L1-PDGFRA rearrangement are mutually exclusive.

11. Context for Decision

This advice was made under the MSAC Terms of Reference:

- Advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported.
- Advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness.
- Advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures.
- Undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

12. Linkages to Other Documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at

http://www.msac.gov.au/internet/msac/publishing.nsf/Content/MSACCompletedAssessments1120-1140