BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ICLUSIG (ponatinib), tyrosine kinase inhibitor

Moderate improvement in the treatment of all phases of chronic myeloid leukaemia (CML) or Ph+ ALL in the presence of the T315I mutation.

Minor improvement in the treatment of Ph+ acute lymphoblastic leukaemia (ALL) in the absence of mutation T315I, in case of resistance or intolerance to dasatinib and when subsequent treatment with imatinib is not clinically appropriate.

No demonstrated improvement in the treatment of all phases of CML in the absence of the T315I mutation, in patients previously treated with one or more tyrosine kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not regarded as appropriate treatments.

Main points

- ICLUSIG has Marketing Authorisation in adults with:
  - chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
  - Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

- Its efficacy was demonstrated in a non-comparative study with, as primary efficacy endpoints, the major cytogenetic response and the major haematological response.

- ICLUSIG is:
  - a first-line treatment for CML and Ph+ ALL with the T315I mutation
  - a next-line treatment for CML and Ph+ ALL patients without the T315I mutation.
  - an alternative to bosutinib (BOSULIF) in the next-line treatment of all phases of CML in the absence of the T315I mutation.

Therapeutic use

- In the chronic phase of CML, the first-line treatment alternatives are imatinib (GLIVEC) and nilotinib (TASIGNA). In patients who are resistant or intolerant to imatinib, the second-line medicines are nilotinib (TASIGNA) and dasatinib (SPRYCEL); in patients who are resistant or intolerant to nilotinib, the second-line treatment is dasatinib. In patients who are resistant or intolerant to imatinib, nilotinib and dasatinib, the last-line treatment is bosutinib or ponatinib.

- In the accelerated phase of CML, the first-line treatment alternatives are nilotinib and dasatinib. In patients who are resistant or intolerant to one of these medicinal products, the second-line treatment consists of administering the other product. In patients who are resistant or intolerant to nilotinib and dasatinib, the last-line treatment is bosutinib or ponatinib.

- In the blast phase of CML, the first-line treatment is dasatinib. In patients who are resistant or intolerant to dasatinib, the last-line treatment is bosutinib or ponatinib.

- In the management of Ph+ ALL, the first-line treatment is imatinib. Dasatinib is a second-line treatment alternative. In patients who are resistant or intolerant to dasatinib, the next-line treatment is ponatinib.

- If the T315I mutation appears in patients with CML or Ph+ ALL, ponatinib is indicated when the appearance of this mutation is discovered.

Clinical data

- A non-comparative phase II study evaluated the efficacy and safety of ponatinib in patients with CML in chronic phase (CP-CML), accelerated phase (AP-CML) or blast phase (BP-CML) or Philadelphia chromosome positive ALL (Ph+ ALL) who were resistant or intolerant to dasatinib or nilotinib or who had the T315I mutation.
  
  The primary efficacy endpoint was:
- the assessment of the major cytogenetic response (MCR) in the first 12 months for patients with CP-CML
- the assessment of the major haematological response (MHR) in the first 6 months for patients with AP-CML, BP-CML or Ph+ ALL.

The results that formed the basis of the Marketing Authorisation of this proprietary medicinal product were derived from a median follow-up of 9.9 months.

For all patients with CP-CML, the major cytogenetic response was observed in 53.9% (144 patients/267) of cases. It was observed in 48.8% (99/203) of cases in the group of patients resistant or intolerant to dasatinib or to nilotinib, and in 70.3% (45 patients/64) of cases in the group of patients with the T315I mutation.

For all study patients with AP-CML, the major haematological response was observed in 57.8% (48 patients/83) of cases. It was observed in 60% (39/65) of cases in the group of patients resistant or intolerant to dasatinib or to nilotinib, and in 50% (9 patients/18) of cases in the group of patients with the T315I mutation.

For all study patients with BP-CML, the major haematological response was observed in 34% (32 patients/94) of cases. It was observed in 35.4% (17 patients/48) of cases in the group of patients resistant or intolerant to dasatinib or to nilotinib, and in 32.6% (15 patients/46) of cases in the group of patients with the T315I mutation.

Efficacy data with 27.9 months’ follow-up showed that about a third of patients included in the study (38% or 172/449) were kept on treatment with ICLUSIG.

In the CP-CML patients who achieved a major cytogenetic response, the median duration of the major cytogenetic response had not yet been achieved.

Because of the large intervals found for the assessment of progression-free survival (ranging from 0.03 to 39 months, mainly for the chronic phase), the measurement of this parameter is fairly imprecise.

The frequency of discontinuations of treatment on account of adverse events was 11.1% in the overall study population (n = 449) and the main events were haematological (thrombocytopenia, neutropenia and anaemia), gastrointestinal (pancreatitis 4.9%) and vascular. The updated safety data with follow-up for 27.9 months show a proportion of discontinuation of treatment on account of adverse events of 15% and an incidence of serious vascular occlusive adverse events of 16%, most of them arterial (13.6%, n = 61).

Prescribing conditions

Initial 6-monthly hospital prescription restricted to oncologists or doctors competent in oncology. Medicine requiring special monitoring during treatment

Benefit of the medicinal product

- The actual benefit* of ICLUSIG is substantial.
- In the absence of the T315I mutation, ICLUSIG does not provide clinical added value** (CAV V) in the current therapeutic strategy for all phases of CML in patients previously treated with one or more tyrosine kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not regarded as appropriate treatments.
- In the absence of the T315I mutation, ICLUSIG provides minor clinical added value (CAV IV) in the current therapeutic strategy for Ph+ ALL in patients who are resistant or intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate.
- In the presence of the T315I mutation, ICLUSIG provides moderate clinical added value (CAV III) in terms of efficacy in patients in all phases of CML or with Ph+ ALL.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".

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