TRANSPARENCY COMMITTEE OPINION SUMMARY

RYDAPT (midostaurin), tyrosine kinase inhibitor

Low clinical benefit in the treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis associated with a second malignant blood disorder (SM-SBD) or mast cell leukaemia (MCL), but no demonstrated clinical advantage in the therapeutic strategy.

Main points

- RYDAPT has been granted a marketing authorisation for the treatment of adults presenting with aggressive systemic mastocytosis (ASM), systemic mastocytosis associated with a second malignant blood disorder (SM-SBD), or mast cell leukaemia (MCL), in monotherapy.
- Efficacy data are limited to one non-comparative phase II study showing an overall response rate of nearly 60%, though lacking any conclusive data showing an increase in overall survival or quality of life.

Therapeutic strategy

- The management of systemic mastocytosis is based on clinical practice guidelines and relies:
- on the one hand, on prophylactic measures for evicting trigger factors associated with symptomatic treatments such as anti-histamine agents, glucocorticoids, sodium cromoglicate or epinephrine in situations of anaphylactic shock;
- and on the other hand, on specific treatments such as debulking agents, for example cladribine, interferon alpha and tyrosine kinase inhibitors such as imatinib. This latter has been granted a marketing authorisation in the United States for aggressive forms of systemic mastocytosis without c-kit D816V mutation, or in the event of an unknown mutation (concerns only 10 to 15% of patients). Polychemotherapy may also be considered for severe forms, or those associated with a second malignant blood disorder.
- These conventional treatments, used outside of the context of their MA, provide an overall response in 30 to 60% of patients, with a significant toxicity profile. Survival prognosis is low.
In some rare cases (young patients in good general condition, with compatible donor and for whom a response was achieved), autologous stem cell transplantation may be proposed.
US guidelines position midostaurin as an alternative treatment after interferon or cladribine failure, like the other treatments undergoing clinical trials.
- Role of the medicinal product in the therapeutic strategy**
Despite the low level of evidence of the available data, RYDAPT monotherapy is a treatment for ASM, whether or not combined with a second malignant blood disorder, or with MCL.
Failing any comparative efficacy data versus available alternatives, in particular cladribine in patients eligible for this treatment (symptomatic forms of ASM without associated blood disorders), the role of RYDAPT relative to cladribine is unknown.

Clinical data

- One non-comparative study included 116 patients, amongst which a large of patients were deemed ineligible by the independent committee and only 89 were selected for endpoint analysis (PEP population), presenting a potential bias, particular in the analysis of the primary endpoint. Approximately 80% of patients suffered from ASM and 18% from MCL.
- The overall response rate (primary endpoint), assessed by an independent committee, was of 59.6% (CI95% [48.6 - 69.8]), including 45% of major responses (of which 21.3% of incomplete responses, 16.9% of purely clinical responses and no complete responses) and 14.6% of partial responses.

- According to the data of the European Public Assessment Report (EPAR), a *post hoc* analysis updated according to the most recent response endpoints suggested an ORR of 28.3% (CI95% [20.2 - 37.6]). The median response duration (major or partial response) was of 31.4 months (CI95% [10.8 - NA]), with a median time to response of 0.3 months (0.1 - 3.7 months). Median progression-free survival was 17 months (CI 95% [10.2 - 24.8]). Median overall survival was 26.8 months (CI 95% [17.6 - 34.7]).
- The most frequently reported adverse events were digestive, with 80.2% nausea, 66.4% vomiting and 56% diarrhoea. Most of these events were mild and considered to be treatment-related. Grade 3/4 adverse events were reported in 88.8% of patients. These were primarily anaemia (25%), thrombocytopenia (12.1%) and fatigue (8.6%). 26.7% experienced cardiac toxicity (of which 6% were grade 3/4). These mainly involved long QT interval, leading to 3 treatment interruptions and heart failures. Treatment interruptions concerned 83.1% of patients, primarily due to disease progression (39.3%) and to adverse effects (24.7%).

Special prescription requirements

- Medicinal product subject to hospital prescription
- Prescription reserved for haematology and oncology specialists, physicians with expertise in blood diseases or oncology, dermatology or internal medicine specialists.

Benefit of the medicinal product

- The actual clinical benefit* of RYDAPT is low.
- RYDAPT, administered in monotherapy, does not provide any improvement in actual clinical benefit** (IACB V) in the management strategy of aggressive systemic mastocytosis (ASM), systemic mastocytosis associated with a second malignant blood disorder (SM-SBD), or mast cell leukaemia (MCL).
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

HAUTE AUTORITÉ DE SANTÉ

This document was drafted on the basis of the Transparency Committee opinion dated 27 June 2018 (CT-16648) available at www.has-sante.fr

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"