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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

MEKINIST (trametinib), protein kinase inhibitor

Moderate improvement as first-line treatment of unresectable or metastatic melanoma, in patients with a BRAF V600 mutation

Main points

- MEKINIST now has Marketing Authorisation in combination with dabrafenib, in the treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation.
- Combining MEKINIST with dabrafenib improves progression-free survival and overall survival in comparison with dabrafenib alone.

Pre-existing indications

- MEKINIST already has Marketing Authorisation as monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- This summary does not cover this indication.

Therapeutic use

- The current management of advanced (unresectable or metastatic) melanoma involves screening patients as soon as they are diagnosed for a BRAF mutation in the tumour.
  If there is a BRAF mutation, the initial treatment consists of targeted therapy with BRAF inhibitors as monotherapy; these are vemurafenib (ZELBORAF) or dabrafenib (TAFINLAR).
  The role of nivolumab and pembrolizumab as alternatives to these targeted therapies is currently debated, and particularly the profile of patients who are likely to receive one of these two treatments as first-line therapy.
- Nivolumab and pembrolizumab are recommended as second-line therapy. The combination dabrafenib + trametinib is not recommended as second-line therapy in patients who have already received a BRAF inhibitor as monotherapy in first-line treatment.
- **Role of the medicinal product in the therapeutic strategy**
  MEKINIST, in combination with dabrafenib (TAFINLAR), is a first-line therapy in the management of unresectable or metastatic melanoma with a BRAF V600 mutation. It has no role as monotherapy in patients with a BRAF V600 mutation.

Clinical data

- In a double-blind, randomised study including 423 patients with unresectable or metastatic melanoma and a BRAF V600 mutation, median progression-free survival (the primary efficacy endpoint) was estimated as 9.3 months in the trametinib + dabrafenib group versus 8.8 months in the dabrafenib group (11.0 months versus 8.8 months in the final analysis): HR = 0.75; 95% CI = [0.57-0.99]; p=0.035. Median overall survival (a secondary endpoint assessed following the hierarchical sequential analysis set out in the protocol) was 25.1 months in the trametinib + dabrafenib group versus 18.7 months in the dabrafenib group: HR = 0.71; 95% CI = [0.55-0.92]; p=0.011.
- In an open-label, randomised study conducted in 704 adults with unresectable or metastatic melanoma and a BRAF mutation, the percentage of patients who died was 28% (100/352) in the trametinib + dabrafenib group and 35% (122/352) in the vemurafenib group: HR = 0.69; 95% CI = [0.53-0.89]; p=0.005 (i.e. p<0.0214 as stipulated for this interim analysis).

Median overall survival was not reached in the trametinib + dabrafenib group. It was estimated as 17.2 months in the vemurafenib group (25.6 months versus 18.0 months in the final analysis).

- The main adverse events that occurred in the trametinib + dabrafenib group, in comparison with the BRAF inhibitor monotherapy group (dabrafenib or vemurafenib), were: fever (53% to 57% versus 21% to 33%), nausea (34% to 35% versus 27% to 36%), vomiting (25% to 29% versus 14% to 15%), arterial hypertension (25% to 26% versus 16% to 24%), diarrhoea (30% to 32% versus 16% to 38%), and chills (31% versus 8% to 17%).
  On the other hand, cutaneous adverse events were less frequently observed with the trametinib + dabrafenib combination versus BRAF inhibitor monotherapy: hyperkeratosis (4% to 7% versus 25% to 35%), alopecia (6% to 9% versus 28% to 39%), hand-foot syndrome (erythrodysesthesia and keratoderma) (4% to 7% versus 25% to 30%), skin papillomas (2% versus 22% to 23%), photosensitivity reactions (4% versus 22%), squamous cell carcinoma (1% versus 5% to 10%) and basal cell carcinoma (3% versus 6%).

Special prescribing conditions

- Medicine for hospital prescription.
- Prescription restricted to cancer treatment and oncology specialists and departments.

Benefit of the medicinal product

- The actual benefit* of MEKINIST is substantial.
- MEKINIST provides moderate clinical added value** (CAV III) in this indication.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 20 January 2016 (CT-14705) and is available at **www.has-sante.fr**

[i] * 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".