pembrolizumab
KEYTRUDA 25 mg/ml,
solution for dilution for infusion
New indication(s)

Adopted by the Transparency Committee on 7 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement of KEYTRUDA (pembrolizumab):

- as monotherapy for the adjuvant treatment of adult patients and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.
- as monotherapy for the treatment of [...] adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

Therapeutic improvement?

Therapeutic improvement in the care pathway in all assessed indications.
Role in therapeutic strategy?

The objective of the therapeutic management of localised-stage melanoma is curative. The first line is based on tumour excision surgery.

The lateral excision margins for primary skin melanoma must be adapted to the depth of melanoma invasion according to the following schedule: safety margins of 0.5 cm for cases of in-situ melanoma, 1 cm for tumour thicknesses >0.1 mm and ≤ 1 mm, 1 to 2 cm for tumour thicknesses > 1.1 mm and ≤ 2 mm, and 2 cm for tumour thicknesses > 2 cm.

The sentinel node procedure is an option in cases of localised melanoma. It helps stage melanomas and provides an independent prognostic marker. However, as there is no evidence of a benefit of this procedure in respect of overall survival, it cannot be considered as a curative therapeutic standard.

Considering the latest developments in adjuvant therapy, alpha interferon may no longer be proposed routinely as an adjuvant treatment given the uncertainties around its benefit linked with the lack of clear indication of the specific dose or treatment duration and with high toxicity.

Its use may be limited for specific cases such as Stage IIC ulcerated primary melanoma and when new authorised medicinal products are not accessible.

Adjuvant locoregional radiotherapy may be considered for some specific cases.

The latest updated version of the NCCN guidelines (2022) in the United States incorporating the findings of the KEYNOTE-716 trial, proposes KEYTRUDA as an adjuvant treatment for patients with Stage IIB and IIC melanoma who have undergone complete resection.

At the metastatic stage, immunotherapy is the conventional first-line treatment.

Paediatric-specific guidelines.

Given the rare nature of paediatric melanoma and the complexity of its treatment, there is currently no standard of care. The treatment of paediatric patients generally follows the same principles as for adult patients. According to the European EXPeRT group guidelines published in 2021, the treatment of paediatric patients must be reviewed by a multidisciplinary team including both paediatric oncologists and adulthood melanoma specialists.

Role of KEYTRUDA in the therapeutic strategy:

KEYTRUDA (pembrolizumab) is an adjuvant treatment of Stage IIB and IIC melanoma with a high risk of recurrence for the adult population and for adolescents from 12 years of age.

KEYTRUDA (pembrolizumab) is an adjuvant treatment of completely resected Stage III melanoma and also the first-line treatment of advanced melanoma (unresectable or metastatic), in paediatrics (adolescents from 12 years) in the same way for the adult population.
**Committee’s conclusions**

**Clinical Benefit**

For Stages IIB/IIC

- Melanoma is a serious life-threatening disease.
- The proprietary medicinal product (pembrolizumab) is a medicinal product intended to prevent recurrence.
- The efficacy/adverse effect ratio is significant.
- There is no recommended drug treatment at this stage of treatment (clinical monitoring).
- This product is a first-line treatment in the context of adjuvant therapy to surgery.

**Public health benefit**

Considering:
- the severity of the disease and its incidence;
- the unmet medical need;
- the response to the identified need;
- evidence of an additional impact on morbidity. With, however, immature overall survival and exploratory quality-of-life data.
- an additional impact on delivery of care;
- the additional impact on the care and/or life pathway which has not been studied;

KEYTRUDA (pembrolizumab) is not likely to have an additional impact on public health.

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Considering all of these elements, the Committee deems that the actual clinical benefit of KEYTRUDA (pembrolizumab) is significant in the indication: KEYTRUDA as monotherapy for the adjuvant treatment of adult and adolescent patients aged 12 years and older with Stage IIB, IIC melanoma and who have undergone complete resection.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use in the indication: KEYTRUDA as monotherapy for the adjuvant treatment of adult and adolescent patients aged 12 years and older with Stage IIB, IIC melanoma and who have undergone complete resection.

**For adolescents aged 12 years and older with advanced melanoma (locally advanced or metastatic)**

- Melanoma is a serious life-threatening disease;
- The proprietary medicinal product KEYTRUDA (pembrolizumab) is a curative medicinal product;
- The efficacy/adverse effect ratio is significant;
- There is no recommended drug treatment for this age group;
- This product is a first-line treatment of advanced-stage melanoma

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HAS - Evaluation and Access to Innovation Department
**Public health benefit**

Considering:

- the severity of the disease and its incidence;
- the unmet medical need;
- the response to the identified need;
- an accepted additional impact on morbidity in light of the extrapolation of the findings of the assessment of pembrolizumab in adults at an advanced stage (unresectable stage IV or III) to adolescents. There is no evidence of an impact on mortality to date.
- an additional impact on delivery of care;
- the additional impact on the care and/or life pathway which has not been studied;

KEYTRUDA (pembrolizumab) is not likely to have an additional impact on public health.

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Considering all of these elements, the Committee deems that the actual clinical benefit of KEYTRUDA (pembrolizumab) is significant in the indication: KEYTRUDA as monotherapy for the treatment of [...] patients and adolescents aged 12 years and older with advanced melanoma (unresectable or metastatic).

The Committee approves inclusion in the list of proprietary medicinal products approved for community use in the indication: KEYTRUDA as monotherapy for the treatment of [...] patients and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

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**For adolescents aged 12 years and older with Stage III melanoma and who have undergone complete resection**

- Melanoma is a serious life-threatening disease.
- The proprietary medicinal product (pembrolizumab) is a medicinal product intended to prevent recurrence.
- The efficacy/adverse effect ratio is significant.
- There is no recommended drug treatment at this stage of treatment (clinical monitoring).
- This product is a first-line treatment in the context of adjuvant therapy to surgery.

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**Public health benefit**

Considering:

- the severity of the disease and its incidence;
- the unmet medical need;
- the response to the identified need;
- an accepted additional impact on morbidity in light of the extrapolation of the findings of the assessment of pembrolizumab in adults at stage III to adolescents. There is no evidence of an impact on mortality to date.
- an additional impact on delivery of care;
- the additional impact on the care and/or life pathway which has not been studied;
KEYTRUDA (pembrolizumab) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of KEYTRUDA (pembrolizumab) is significant in the indication: KEYTRUDA as monotherapy for the treatment of [...] patients and adolescents aged 12 years and older with Stage III melanoma and who have undergone a complete resection.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use in the indication: KEYTRUDA as monotherapy for the treatment of [...] patients and adolescents aged 12 years and older with Stage III melanoma and who have undergone a complete resection.

Clinical Added Value

For Stages IIB/IIC (population ≥12 years)

Considering evidence in a randomised placebo-controlled study:
- of superiority of pembrolizumab on the primary outcome measure, recurrence-free survival where HR=0.65 (95% CI: [0.46; 0.92], p=0.0066). The breakdown by event type suggests that the benefit is essentially through the reduction in the risk of distant metastasis (4.7% vs 7.8%).
- the inability to draw a conclusion on an effect on overall survival due to the immaturity of the data available (ranked secondary outcome measure),
- treatment considered to be similar for both adults and adolescents. The efficacy findings of the KEYNOTE-716 study only included 2 adolescents, the efficacy data for adults were accepted as suitable for extrapolation to adolescents aged 12 years and older,

the Committee deems that, based on the data currently available, KEYTRUDA (pembrolizumab) provides minor clinical added value (CAV IV) as monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC melanoma and who have undergone complete resection.

For resectable Stage III and advanced stages among adolescents aged 12 years and older (unresectable or metastatic melanoma)

Considering:
- treatment considered to be similar for both adults and adolescents,
- the extrapolation to adolescents of the finding of the assessment of pembrolizumab in adults at resectable Stage III and advanced stages (unresectable or metastatic melanoma),
- the safety data from the KEYNOTE-051 study,

the Committee deems that KEYTRUDA (pembrolizumab) provides for adolescents in the same way as for adults:
- moderate clinical added value (CAV III) for the treatment of resectable Stage III melanoma,
- minor clinical added value (CAV IV) for the treatment of advanced stage melanoma (un-resectable or metastatic melanoma).