EMA/568014/2018 Rev.1
EMEA/H/C/WS/1278

Update of 21 September 2018:

The company that applied to change the marketing authorisations of Opdivo and Yervoy has requested a re-examination of the CHMP's July 2018 opinion. Upon receipt of the grounds of the request, the CHMP will re-examine its opinion and issue a final recommendation.

27 July 2018

Refusal of a change to the marketing authorisations for Opdivo (nivolumab) and Yervoy (ipilimumab)

On 26 July 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisations for the medicinal products Opdivo and Yervoy. The change concerned adding the use of both medicines in combination for the treatment of renal cell carcinoma (kidney cancer).

The company that applied for the change to the authorisation is Bristol-Myers Squibb Pharma EEIG. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What are Opdivo and Yervoy?

Opdivo and Yervoy are cancer medicines. They contain the active substances nivolumab and ipilimumab respectively.

Opdivo has been authorised since June 2015. It is already used on its own to treat renal cell carcinoma in patients who have previously been treated with other cancer medicines. It is also used to treat the following other cancers: melanoma (a type of skin cancer), non-small cell lung cancer, classical Hodgkin lymphoma (a blood cancer), squamous cell cancer of the head and neck, and urothelial (bladder) cancer.

Yervoy has been authorised since July 2011. It is used to treat adults with advanced melanoma.

Further information on Opdivo and Yervoy's current uses can be found on the Agency's website.

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What were Opdivo and Yervoy expected to be used for?

Opdivo and Yervoy were also expected to be used together in patients with previously untreated advanced renal cell carcinoma that was considered to be of moderate or high risk of worsening.

How do Opdivo and Yervoy work?

The active substance in both medicines, nivolumab and ipilimumab, are monoclonal antibodies, a type of protein that has been designed to recognise and attach to a specific structure.

Nivolumab attaches to a receptor called PD-1 which is found on certain cells of the immune system called T cells. Cancer cells can produce proteins (PD-L1 and PD-L2) that attach to this receptor and switch off the activity of the T cells, preventing them from attacking the cancer. By attaching to the receptor, nivolumab prevents PD-L1 and PD-L2 from switching off the T cells, thereby increasing the ability of the immune system to kill cancer cells.

Ipilimumab attaches to and blocks the activity of CTLA-4, a protein that controls the activity of T cells. By blocking CTLA-4, ipilimumab causes activation and increase of T cells, which enter into tumours and kill the tumour cells.

What did the company present to support its application?

The company presented the results of a study involving 1,096 patients with previously untreated advanced renal cell carcinoma. The study compared treatment with Opdivo and Yervoy versus treatment with another cancer medicine, sunitinib. The study looked at the patients' response to treatment and how long patients lived, or lived without their disease getting worse.

What were the CHMP's main concerns that led to the refusal of the change to the marketing authorisation?

Although improvements in survival were seen in previously untreated patients given the combination of Opdivo and Yervoy compared with sunitinib, there was no evidence showing if Yervoy contributed to these results and if so, how much. It is known that Opdivo alone produces benefit in previously treated patients with renal cell carcinoma. This means that the CHMP had no way to know if the addition of Yervoy to Opdivo treatment produced additional benefit. At the same time it was clear that combination with Yervoy resulted in more side effects than are seen with Opdivo alone.

Combination treatments can provide benefits over and above the use of single medicines, and may be a way to address unmet medical needs. However, it is vital that the contribution of each component of the combination, and its appropriate dose, is properly established and justified to avoid giving unnecessary or ineffective treatments. This is particularly true if the patient is exposed to additional, potentially severe side effects.

Therefore, the CHMP considered that in this case the combination could not be approved because of the lack of knowledge of the contribution of Yervoy.

What consequences does this refusal have for patients in clinical trials?

The company informed the CHMP that there are no consequences for patients who are receiving Opdivo and Yervoy for renal cell carcinoma in clinical trials.

If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.

What is happening with Opdivo or Yervoy for treatment of other diseases?

There are no consequences on the use of either medicine in their authorised indications.