16 November 2018
EMA/799169/2018
EMEA/H/C/WS1278

Positive opinion on the change to the marketing authorisation for Opdivo (nivolumab) and Yervoy (ipilimumab)

Outcome of re-examination

On 15 November 2018, the Committee for Medicinal Products for Human Use (CHMP) recommended that a change to the marketing authorisation for the medicinal products Opdivo (nivolumab) and Yervoy (ipilimumab) be granted. The change concerns the use of both medicines together to treat renal cell carcinoma (kidney cancer). The company that applied for the change to the authorisation is Bristol-Myers Squibb Pharma EEIG.

On 26 July 2018, the CHMP had originally adopted a negative opinion for the use of Opdivo and Yervoy for the treatment of renal cell carcinoma. At the request of the company, the CHMP re-examined its opinion. Following the re-examination, the CHMP adopted a final positive opinion on 15 November 2018 recommending that the change to the marketing authorisation be granted for Opdivo and Yervoy, but requested the company to conduct a study to collect further data.

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 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 are Opdivo and Yervoy to be used for?

Opdivo and Yervoy are to be used together in patients with previously untreated advanced renal cell carcinoma that is 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 main 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 initial negative opinion?

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.

Therefore, at that point in time, the CHMP considered that the combination could not be approved because of the lack of knowledge of the contribution of Yervoy.

What happened during the re-examination?

During the re-examination, the CHMP looked again at all the data and consulted a group of cancer experts and patients with cancer. The CHMP also discussed the possibility to request that further data be collected following the authorisation of the combination.

What were the conclusions of the CHMP following the re-examination?

The CHMP considered that the results from the main study comparing Opdivo and Yervoy with sunitinib showed a clinically important increase in patients' survival with the combination, and side effects were considered acceptable. Although the precise contribution of Yervoy was not clear, the CHMP re-assessed data from other non-clinical and clinical studies, including studies with the combination in

relevant other cancer types, and considered that the benefit of Yervoy in the combination has been sufficiently demonstrated. The CHMP was of the opinion that the benefits of the combination largely outweigh its risks and therefore recommended granting the change to the marketing authorisation. However, the company must conduct a study to determine the precise contribution of Yervoy in the combination and if the risks could be further minimised.