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Date 21 September 2020
Subject Package advice avelumab in combination with axitinib

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Our reference
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Dear Ms van Ark,

In this letter, Zorginstituut Nederland advises you about avelumab in combination with axitinib as a first-line treatment for adult patients with advanced renal cell carcinoma.

The reason for this advice was the placement of avelumab in the lock procedure for expensive medicinal products.

The Zorginstituut has assessed avelumab in combination with axitinib on the basis of the four package criteria¹: effectiveness², cost-effectiveness³, necessity and feasibility. Through this letter, I would like to inform you about the result of the full weighting of these package criteria. The Zorginstituut advises you not to include avelumab in combination with axitinib in the insured package.

I will explain the advice in more detail below.

General

At your request, the Zorginstituut assesses whether new care should be part of the insured package. The Zorginstituut bases its decision on the point of view of the basic insured package paid from joint premiums. The Zorginstituut is advised by two independent committees: the Scientific Advisory Council (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness, and the Package Advisory Committee (ACP) for the social assessment. The Zorginstituut has also consulted concerned parties during the assessment process.

Integral package criteria weighting

First of all, the Zorginstituut lists the conclusions from the study. In a randomized study (JAVELIN Renal 101), avelumab in combination with axitinib was compared with sunitinib, which was the standard treatment at the time of the study. An interim data analysis after 19 months of follow-up shows that avelumab in combination with axitinib extends the median progression-free survival rate by 5.3 months to 13.3 months. For the standard treatment with

¹ Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

² Current state of science and practice assessment: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

³ Cost-effectiveness report (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

sunitinib, the progression-free survival rate was 8 months. The probability of progression-free survival has been statistically significantly increased compared to sunitinib (the hazard ratio (HR) was 0.69; 0.56-0.84). The difference in progression-free survival rates and the chance of progression-free survival meet the PASKWIL criteria that the Oncological Medicines Assessment (*BOM*) Committee has adopted for clinically relevant effects.

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Although the combination of avelumab with axitinib meets the legal term 'established medical science and medical practice', the Zorginstituut has identified a number of uncertainties:

The JAVELIN Renal 101 study has not yet shown that this progression-free survival leads to a better survival for the patient. In addition, the progression-free survival has been demonstrated relative to sunitinib. Since two other combinations of medicinal products (pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab) are preferred nowadays, sunitinib is being used less in practice.

It was not possible to make a comparison between these three combinations of medicinal products, either directly or indirectly. This means that it is uncertain whether avelumab in combination with axitinib has added value for the patient, compared to the existing alternatives. The results also do not (yet) answer the question of the optimal treatment algorithm and for which patient group the treatment is most appropriate.

The BOM Committee gives a provisional positive but reserved advice:

The difference in progression-free survival and the chance of progression-free survival are sufficient for a positive advice. The (yet) unproven gain in overall survival is reason for the BOM commission to label its positive advice for avelumab in combination with axitinib 'provisional'. Due to the lack of information about the optimal treatment algorithm and the high costs, the provisional positive advice is also reserved. When data about the demonstrated gains for the overall survival become available, the BOM commission will re-evaluate the provisional advice.

On behalf of the professional group of medical experts, the NVMO indicates that the absence of avelumab in combination with axitinib from the arsenal of available treatment does not harm a specific patient group. Pembrolizumab in combination with axitinib is now included in the insured package and available to the patient. The occupational group has also expressed a preference for pembrolizumab in combination with axitinib over avelumab in combination with axitinib.

The professional group of medical experts currently has no answer to the question of what is the optimal treatment algorithm for patients with metastatic renal cell carcinoma. Mature data from the JAVELIN Renal 101 study, as well as mature data from other ongoing studies of other medicinal products and real-life data collection, may provide an answer to this.

Package advice

Avelumab in combination with axitinib as a first-line treatment for patients with advanced renal cell carcinoma meets the established medical science and medical practice, but there are many uncertainties about the added value of the combination avelumab with axitinib for the indication mentioned. I will summarize this again:

- The data are not yet sufficient to be able to make a decision about the effect of avelumab in combination with axitinib on overall survival.
- The added value of avelumab in combination with axitinib in the treatment arsenal is uncertain because it has not been compared to the current standard treatment.
- There are no indications that the combination of avelumab with axitinib has

- added value for specific patient groups.
- Due to the arrival of new treatments and the already existing options, it is still uncertain what the treatment landscape for the mentioned indication will develop.
- The professional group of medical experts does not yet have a clear view of the optimal treatment algorithm.

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The Zorginstituut recommends the following:

The Zorginstituut advises not to include avelumab in combination with axitinib in the insured package for the indication mentioned above.

A reassessment is possible when there is certainty about the effect of avelumab in combination with axitinib on the overall survival gain and the position of this combination within the treatment algorithm for renal cell carcinoma. The Zorginstituut therefore calls on the professional group of medical experts to reconsider their opinion on the place for this combination in the treatment of adult patients with advanced renal cell carcinoma within one year of the availability of new data on overall survival gains. The Zorginstituut would also like to see an answer to the question of what the optimal treatment algorithm is for the indication mentioned.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board