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Questions and answers on the review of Avastin (bevacizumab) in the treatment of metastatic breast cancer

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended that Avastin, when used to treat metastatic breast cancer, should only be used in combination with the taxane paclitaxel. This follows a review¹ of Avastin in combination with taxanes, where the Committee concluded that Avastin should no longer be used in combination with another taxane, docetaxel. The Committee also adopted a negative opinion on the proposed use of Avastin in combination with capecitabine in metastatic breast cancer.

What is Avastin?

Avastin is an anticancer medicine that contains the active substance bevacizumab. It is used in combination with other anticancer medicines to treat cancers of the colon, rectum, lung, kidney or breast that are either advanced or metastatic (spread to other parts of the body). For breast cancer, it is used in combination with paclitaxel or docetaxel (anticancer medicines belonging to the class called 'taxanes', which inhibit cell division) when the cancer has become metastatic.

Bevacizumab is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a specific structure (called an antigen) found on certain cells or circulating in the body. Bevacizumab attaches to a protein that circulates in the blood and makes blood vessels grow, called vascular endothelial growth factor (VEGF), and stops it having an effect. As a result, the cancer cells cannot develop their own blood supply and are starved of oxygen and nutrients, helping to slow down the growth of tumours.

Avastin has been authorised in the EU since 12 January 2005 and is marketed in all EU Member States as well as Norway and Iceland.

Why was the use of Avastin in metastatic breast cancer reviewed?

In December 2009, the company that markets Avastin submitted a request to the EMA to extend Avastin's indication in metastatic breast cancer to include combination treatment with capecitabine (another anticancer medicine). While assessing this proposed new indication, the CHMP noted that the

¹ Following the procedure under Article 20 of Regulation (EC) No 726/2004.

data submitted included a sub-group of patients receiving Avastin with taxanes. Although this study was not specifically designed to investigate Avastin with taxanes, the results among this sub-group showed a negative trend in overall survival (the average length of time the patients lived), which gave rise to concern. The EMA therefore considered that further in-depth analysis of the issue was appropriate, and the CHMP carried out a review of the use of Avastin with taxanes in metastatic breast cancer. This review was undertaken in parallel with the CHMP assessment of the proposed new indication for combination treatment with capecitabine.

Which data has the CHMP reviewed?

To assess the proposed new indication for Avastin with capecitabine, the Committee looked at the results of a main study in women with metastatic breast cancer to investigate the effect of adding Avastin or placebo to capecitabine or to other standard cancer treatments, including taxanes. It also considered the results of other studies in metastatic breast cancer which included patients receiving Avastin with capecitabine.

For the review of Avastin in combination with taxanes, the Committee looked at all the relevant data including the sub-group of patients receiving taxanes in the capecitabine study, as well as the data from the two main studies which supported the original indication with paclitaxel and docetaxel. The CHMP also consulted a group of experts in cancer treatment.

What are the conclusions of the CHMP?

For capecitabine, the CHMP found that although the main study showed that adding Avastin produced a modest improvement in progression-free survival (how long patients lived without their disease getting worse), no meaningful effects were observed for other measurements such as overall survival or health-related quality of life. As capecitabine is aimed at patients for whom a relatively mild treatment is appropriate, the increased toxicity of adding Avastin was also considered important. Therefore, the Committee concluded that the benefits of this combination treatment did not outweigh the risks and the new indication could not be approved.

For paclitaxel, the CHMP noted that adding Avastin has been convincingly shown to prolong progression-free survival without a negative effect on overall survival, and the new study data support this conclusion. Therefore, the Committee concluded that the benefit-risk balance for this combination treatment remains positive.

However, for docetaxel, the data from the main study showed that adding Avastin produced a much smaller increase in progression-free survival than for paclitaxel. In addition, the sub-group data from the recently submitted study showed a lower increase in progression-free survival than the main study and have added some uncertainty about the effect on overall survival so that a detrimental effect cannot be excluded. Therefore, the Committee concluded that the benefits did not outweigh the risks and that the authorisation for this combination treatment should be withdrawn.

The CHMP therefore recommended that for the treatment of breast cancer Avastin should only be used in combination with paclitaxel. It recommended modifying the product information accordingly.

The full changes made to the information to doctors and patients are detailed [here](#).

What are the recommendations for patients and prescribers?

- Doctors may continue to prescribe Avastin in combination with paclitaxel for metastatic breast cancer patients. Patients receiving this combination should continue their treatment as normal.

- Doctors should be aware that Avastin is no longer recommended for use in combination with docetaxel to treat metastatic breast cancer.
- Patients already receiving Avastin in combination with docetaxel for metastatic breast cancer should discuss their ongoing treatment with their doctor.
- Patients receiving Avastin in approved indications for other cancers should continue their treatment as normal.
- Patients who have any questions should speak to their doctor.

A European Commission decision on this opinion will be issued in due course.

The current European public assessment report for Avastin can be found on the Agency's website [ema.europa.eu/Find_medicine/Human_medicines/European Public Assessment Reports](http://ema.europa.eu/Find_medicine/Human_medicines/European_Public_Assessment_Reports).