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Refusal of the marketing authorisation for Doxolipad (doxorubicin)

Outcome of re-examination

On 31 January 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Doxolipad, intended for the treatment of breast and ovarian cancer. The company that applied for authorisation is TLC Biopharmaceuticals B.V.

The company requested a re-examination of the initial opinion. After considering the grounds for this request, the CHMP re-examined the opinion, and confirmed the refusal of the marketing authorisation on 29 May 2019.

What is Doxolipad?

Doxolipad is a cancer medicine that contains the active substance doxorubicin. It was to be available as a concentrate to be made into a solution for infusion (drip) into a vein.

Doxolipad was developed as a 'hybrid medicine'. This means that Doxolipad was intended to be similar to a 'reference medicine' already authorised in the European Union called Adriamycin. The difference between the products is that in Doxolipad the active substance doxorubicin is enclosed in tiny fatty spheres called liposomes (see below for more details). For more information on hybrid medicines, see the question-and-answer document here.

What was Doxolipad expected to be used for?

Doxolipad was expected to be used to treat metastatic breast cancer in patients at risk of heart problems ('metastatic' means the cancer has spread to other parts of the body), and cancer of the ovary in women whose previous treatment including a platinum-based cancer medicine has stopped working.

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How does Doxolipad work?

The active substance in Doxolipad, doxorubicin, is a cytotoxic medicine that belongs to the group 'anthracyclines'. It works by interfering with the DNA within cells, preventing them from making more copies of DNA and making proteins. This means that cancer cells cannot divide and they eventually die.

Doxorubicin has been available since the 1960s. In Doxolipad, it is enclosed in 'pegylated liposomes' (tiny fatty spheres that are coated with a chemical called polyethylene glycol). The liposomes reduce the rate at which the active substance is broken down, allowing it to circulate in the blood for longer. They also reduce the medicine's effects on non-cancer cells, so it is less likely to cause some side effects.

What did the company present to support its application?

The applicant presented data from the scientific literature, and data from studies conducted in experimental models, including comparisons with another authorised doxorubicin medicine, Caelyx, which contains doxorubicin in pegylated liposomal form.

Because Doxolipad was developed as a hybrid medicine, the company also presented the results of a study carried out to investigate whether it is 'bioequivalent' to Caelyx. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Although the reference medicine for Doxolipad is Adriamycin, this could not be used in the bioequivalence study because it contains doxorubicin in a different form (not enclosed in pegylated liposomes). Therefore, Caelyx was used instead.

What were the CHMP's main concerns that led to the refusal?

The results of the bioequivalence study showed that Doxolipad is comparable to Caelyx in terms of 'liposome-encapsulated doxorubicin', but failed to show that the amount of 'free doxorubicin' is the same for the two medicines.

Therefore, the CHMP was of the opinion that there was insufficient evidence to show that Doxolipad was bioequivalent to Caelyx, and it was not possible to establish that the benefits of Doxolipad outweigh its risks. On that basis, the CHMP recommended that Doxolipad be refused marketing authorisation.

The recommendation was confirmed after re-examination.

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

The company informed the CHMP that there are no ongoing clinical trials with Doxolipad in the EU.