



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Questions and answers

Refusal of the marketing authorisation for Istodax (romidepsin)

Outcome of re-examination

On 19 July 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Istodax, intended for the treatment of peripheral T-cell lymphoma. The company that applied for authorisation is Celgene Europe Ltd.

The applicant requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 15 November 2012.

What is Istodax?

Istodax is a medicine that contains the active substance romidepsin. It was to be available as a powder and solvent to be made into a solution for infusion (drip into a vein).

What was Istodax expected to be used for?

Istodax was expected to be used for the treatment of adults with peripheral T-cell lymphoma that no longer responds to or has come back after at least two previous therapies. Peripheral T-cell lymphoma is a cancer of a type of white blood cells called T-cells, which are part of the immune system.

Istodax was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 28 October 2005 for the treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated).



How is Istodax expected to work?

The active substance in Istodax, romidepsin, is expected to work by blocking the activity of proteins called histone deacetylases, which are involved in turning genes 'on' and 'off' within cells. The exact way that romidepsin works in peripheral T-cell lymphoma is not known, but its effects on genes that regulate cell proliferation and cell death are expected to lead to a reduction in the rate of growth and division of the cancer cells.

What did the company present to support its application?

The effects of Istodax were first tested in experimental models before being studied in humans.

The company presented the results from one main study with Istodax involving 131 patients with peripheral T-cell lymphoma who had received previous treatment. In the study, Istodax was not compared with any other treatment. The main measure of effectiveness was based on the proportion of patients who had a complete response to treatment.

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

In July 2012, the CHMP noted that the main study showed that Istodax had anti-tumour activity in terms of patients' response to treatment. However, the fact that Istodax was not compared with any other treatment did not allow the Committee to conclude on the clinical benefit of the medicine in terms of overall survival (how long the patients lived) or progression-free survival (how long the patients lived without their disease getting worse). The CHMP also noted that, due to an oversight, the company failed to provide an adequate certificate of Good Manufacturing Practice for the site where the medicine is manufactured, which is legally required.

In November 2012, following the re-examination, the CHMP removed its concern over the certificate of Good Manufacturing Practice, but retained its other concerns. In particular, the Committee could not conclude on the clinical benefit of the medicine. As it was not compared with any other treatment, it was not possible to establish whether the observed effects were due to the medicine or due to the disease characteristics of patients in the main study. Therefore it was not possible to conclude that the benefits of the medicine outweigh the risks and the CHMP confirmed its initial negative opinion.

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that there are no consequences for patients currently included in clinical trials or compassionate use programmes with Istodax.

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

The summary of the opinion of the Committee for Orphan Medicinal Products for Istodax can be found on the Agency's website: [ema.europa.eu/Find medicine/Human medicines/Rare disease designation](http://ema.europa.eu/Find%20medicine/Human%20medicines/Rare%20disease%20designation).