European Medicines Agency

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QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE MARKETING AUTHORISATION
for
LENALIDOMIDE CELGENE EUROPE

International non-proprietary name (INN): ***lenalidomide***

On 24 January 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Lenalidomide Celgene Europe 5 mg and 10 mg capsules, intended for the treatment of anaemia due to myelodysplastic syndromes. The company that applied for authorisation is Celgene Europe Limited. The applicant requested a re-examination of the opinion. After having considered the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 30 May 2008.

What is Lenalidomide Celgene Europe?
Lenalidomide Celgene Europe is a medicine containing the active substance lenalidomide. Lenalidomide has been authorised in the European Union since June 2007 under the name Revlimid, for the treatment of multiple myeloma. Multiple myeloma is a cancer of the plasma cells in the bone marrow.

What was Lenalidomide Celgene Europe expected to be used for?
Lenalidomide Celgene Europe was expected to be used to treat anaemia (low red blood cell counts) caused by myelodysplastic syndromes, a group of conditions where too few blood cells are produced by the bone marrow. In some cases, myelodysplastic syndromes can lead to the development of acute myeloid leukaemia (a type of cancer affecting the white blood cells).
Lenalidomide Celgene Europe was to be used in patients who were dependent on receiving blood transfusions to treat their anaemia and whose myelodysplastic syndromes were associated with a specific genetic mutation (deletion of part of chromosome number 5), and with a low to intermediate risk of progressing to leukaemia or death.
Lenalidomide Celgene Europe was designated as an orphan medicinal product in myelodysplastic syndromes on 8 March 2004.

How is Lenalidomide Celgene Europe expected to work?
The active substance in Lenalidomide Celgene Europe, lenalidomide, is an immunomodulating agent. This means that it affects the activity of the immune system (the body's natural defences). The exact way lenalidomide works in myelodysplastic syndromes is not known, but it is thought to block the growth of tumour cells in the bone marrow, while allowing for the growth of normal bone marrow cells, including the cells that produce red blood cells.

What documentation did the company present to support its application to the CHMP?
The effects of Lenalidomide Celgene Europe were first tested in experimental models before being studied in humans. Its effectiveness was studied in one main study, carried out in a number of hospitals and clinics ('sites') in the United States of America and Germany, and involving 148 patients with transfusion-dependent anaemia, low or intermediate (level 1) risk myelodysplastic syndromes and a deletion of part of chromosome 5 ('5q deletion'). The study looked at the effects of treatment with a daily dose of 10 mg Lenalidomide Celgene Europe either given continuously and or as a cycle (three weeks on, one week off). The main measure of effectiveness was the proportion of patients who

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became ‘transfusion independent’ (anaemia controlled without the need for a blood transfusion in an 8-week period).

What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?
The CHMP had concerns over the way the main study was carried out, which meant that the safety of Lenalidomide Celgene Europe was difficult to assess. In particular, because the study did not compare the medicine to any other treatment, it was difficult to determine if treatment with Lenalidomide Celgene Europe increased the risk of progression to acute myeloid leukaemia. In addition, an inspection of one of the sites where the main study was carried out showed some concerns with the way the results were recorded, and this can further affect the reliability of the main study.
At that point in time, the CHMP was of the opinion that the benefits of Lenalidomide Celgene Europe in the treatment of anaemia due to myelodysplastic syndromes did not outweigh its potential risks. Hence, the CHMP recommended that Lenalidomide Celgene Europe be refused marketing authorisation. The CHMP refusal was confirmed after re-examination.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Lenalidomide Celgene Europe?
The company informed the CHMP that it will continue to make lenalidomide available for patients included in clinical trials or compassionate use programmes. 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.

What is happening for Revlimid used for the treatment of multiple myeloma?
There are no consequences of this refusal on the use of Revlimid, which also contains lenalidomide, in its authorised indication. The balance of benefits and risks for Revlimid remains unchanged.