European Medicines Agency

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QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE MARKETING AUTHORISATION
for
OPGENRA

International non-proprietary name (INN): ***eptotermin alfa***

On 26 June 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 Opgenra 3.5 mg powder for suspension for implantation, intended for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis. The company that applied for authorisation is Howmedica International S. de R. L. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Opgenra?
Opgenra is a medicine that contains the active substance eptotermin alfa. It was to be supplied as two vials, one containing eptotermin alfa and another containing a substance called carmellose. The two powders were to be made up into a suspension with a putty-like consistency, which was to be implanted in the body.
Eptotermin alfa has been authorised in the European Union since May 2001 in Osigraft. Osigraft is used to repair fractures (breaks) of the tibia (shin bone).

What was Opgenra expected to be used for?
Opgenra was expected to be used in adults with spondylolisthesis. This is a condition where one lumbar vertebra (one of the bones in the lower part of the spine) has slipped forward so that it is not in line with the vertebra below it. This can cause pain, instability, and problems due to pressure on the nerves, including tingling, numbness, weakness and difficulty controlling certain muscles. Spondylolisthesis can be treated using surgery to fuse (join) the vertebrae above and below the site where the slip occurred.
Opgenra was expected to be used in patients who have previously had surgery using an autograft (a bone graft taken from their own body, usually the hip) which has failed, or when an autograft is not possible or is unlikely to be effective. The surgeon was to implant Opgenra directly between the two vertebrae to help new bone develop and to make the vertebrae fuse together.

How is Opgenra expected to work?
The active substance in Opgenra, eptotermin alfa, acts on the bone. It is a copy of a protein called osteogenic protein 1, also known as bone morphogenic protein 7 (BMP-7), which is produced naturally by the body and helps the formation of new bone tissue. When implanted, eptotermin alfa stimulates the formation of new bone. This was expected to help fuse the two vertebrae in patients having surgery for spondylolisthesis.
Eptotermin alfa is produced by a method known as 'recombinant DNA technology': it is made by cells that have received a gene (DNA), which makes them able to produce eptotermin alfa. The replacement eptotermin alfa acts in the same way as naturally produced BMP-7.

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What documentation did the company present to support its application to the CHMP?
The effects of Opgenra were first tested in experimental models before being studied in humans.
The effectiveness of Opgenra has been studied in one main study involving 336 patients who needed spinal fusion surgery for spondylolisthesis who were eligible for an autograft. The study compared surgery using Opgenra and surgery using bone autografts. The main measure of effectiveness was the number of patients whose treatment was successful after two years. Treatment was defined as 'successful' when bone could be seen between the affected vertebrae on X-rays, and the patient had shown improvement in disability, with no need for further treatment of the spine, no serious side effects and no worsening of the symptoms caused by pressure on the nerves.

What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?
The CHMP had concerns over the effectiveness of Opgenra because the results of the main study showed that Opgenra was not as effective as bone autografts in patients with spondylolisthesis who were eligible for an autograft, and no additional data were presented to support the effectiveness of Opgenra in patients who had previously had an autograft, or for whom an autograft was not possible or was unlikely to be effective. The CHMP was also concerned that the main study had major flaws, including changes in the way the results were analysed after the study had finished.
No data were available on the safety of Opgenra in the patients for whom it was intended, and there were concerns over inflammation at the site of application. In addition, there was only limited information available on the safety of eptotermin alfa in countries where it has been on the market for this indication.
At that point in time, the CHMP was of the opinion that the benefits of Opgenra for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis did not outweigh its risks. Hence, the CHMP recommended that Opgenra be refused marketing authorisation.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Opgenra?
The company did not inform the CHMP whether there are any consequences for patients currently included in clinical trials or compassionate use programmes with Opgenra. 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 Osigraft for the repair of fractures of the tibia?
There are no consequences on the use of Osigraft in its authorised indication, for which the balance of benefits and risks remains unchanged.