European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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Questions and answers on the marketing authorisation for Opgenra

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

On 23 October 2008, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a 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.

On 26 June 2008, the CHMP had adopted a negative opinion for patients in whom autograft (a bone graft taken from their own body, usually the hip) has failed, is not possible or is unlikely to be effective. At the request of the applicant, the Committee started a re-examination of its opinion. Following the re-examination, the CHMP adopted a final positive opinion on 23 October 2008, but for a restricted indication, in patients in whom autograft has failed or who must not undergo the procedure.

What is Opgenra?

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

What is Opgenra to be used for?

Opgenra is 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 is to be used only in patients who have previously had surgery using an autograft that has failed or when an autograft must not be carried out. The surgeon will apply Opgenra directly along each side of the two vertebrae to help new bone develop and to make the vertebrae fuse together.

How does Opgenra 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 helps to 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 and 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 initially 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 for patients in whom autograft has failed, is not possible or is unlikely to be effective did not outweigh its risks. Hence, the CHMP recommended that Opgenra be refused marketing authorisation.

What happened during the re-examination?
During the re-examination, the CHMP took advice from a group of experts specialising in the treatment of the bones, and looked at additional analyses of the information on Opgenra's safety and effectiveness. The expert group confirmed that the main study did not show a benefit of Opgenra over autograft, and agreed that compelling data on the medicine's benefits had not been presented for the broader or for the restricted indication.
The CHMP also looked at evidence presented by the company more extensively during the re-examination. This evidence came from the published scientific literature on patients treated in the United States of America (USA), where the medicine has been approved as a medical device for spinal fusion since 2004 under a special scheme that ensures close monitoring of the product's safety.

What were the conclusions of the CHMP following the re-examination?
After taking the expert group's views and all of the data presented into account, the CHMP concluded that although Opgenra is slightly less effective than autograft, it could be of benefit for the very restricted group of patients, as supported by evidence from the USA. Opgenra also had advantages over autograft, including shorter operations, less blood loss and less pain. There was, however, insufficient evidence to support the medicine's use in patients in whom autograft is unlikely to be effective.
The CHMP and the expert group agreed that the side effects of Opgenra, including inflammation, were not a major concern, especially because there is a large amount of information available from its use in the USA and from the use of Osigraft, both in the EU and in other countries.
Therefore, the Committee concluded that the benefits of Opgenra outweigh its risks for the treatment of spondylolisthesis in patients in whom autograft has failed or who must not undergo the procedure and recommended that it be given a marketing authorisation.