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Refusal of the marketing authorisation for Exondys (eteplirsen)

Outcome of re-examination

On 31 May 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Exondys, intended for the treatment of Duchenne muscular dystrophy. The company that applied for authorisation, AVI Biopharma International Ltd, requested a re-examination of the CHMP's opinion on 1 June 2018.

After considering the grounds for this request, the CHMP re-examined the opinion, and confirmed the refusal of the marketing authorisation on 20 September 2018.

What is Exondys?

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

What was Exondys expected to be used for?

Exondys was expected to be used for treating Duchenne muscular dystrophy (DMD) in patients aged from 4 years with mutation (change) in the DMD gene that allows treatment involving 'exon 51 skipping'. This means that the patients' DMD gene can make a working form of the dystrophin protein when a part of the gene called exon 51 is not used.

Exondys was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 3 December 2008 for the treatment of DMD. Further information on the orphan designation can be found here.

How does Exondys work?

Patients with DMD do not produce a protein called dystrophin. The medicine allows exon 51 to be skipped over and so promote the production of a shortened form of dystrophin. This shortened protein is expected to act in a similar way to normal dystrophin, helping the body to make up for the lack of dystrophin, and so relieve the symptoms of DMD.

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What did the company present to support its application?

The company presented the results of two main studies involving 12 boys aged 7 to 13 years with DMD who had a genetic mutation amenable to exon 51 skipping. In the first study, Exondys was compared with placebo (a dummy treatment) for the first 24 weeks, after which all patients were treated with Exondys. The main measure of effectiveness was the change in the distance walked during a 6-minute walking test after 24 weeks.

The second study, an extension of the first one, involved the same patients who were all treated with Exondys for another 4 years.

The company also compared the results of these studies with those from a variety of historical data.

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

The CHMP was concerned that the main study, which involved just 12 patients, did not compare Exondys with placebo beyond 24 weeks, during which there was no meaningful difference between Exondys and placebo in the 6-minute walking distance. The methods for comparing results of the main studies with historical data were not satisfactory for showing that the medicine was effective. The Committee considered further data were needed to show that the very low amounts of shortened dystrophin produced as a result of Exondys treatment bring lasting benefits relevant to the patient.

Therefore, the CHMP was of the opinion that the balance of benefits and risks of Exondys in the treatment of DMD could not be established and recommended that the marketing authorisation be refused. The CHMP refusal 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 consequences for patients currently included in clinical trials with Exondys.

If you are in a clinical trial and need more information about your treatment, contact the doctor who is treating you in the trial.