Conditional approval of ataluren for Duchenne MD recommended in Europe

Ataluren is set to be the first ever drug licenced to treat the underlying genetic cause of Duchenne muscular dystrophy (MD). The European Medicines Agency (EMA) has received a recommendation from its advisory committee that ataluren should be given conditional approval.

Ataluren, which will now be known by the name “Translarna”, has been developed by PTC Therapeutics to overcome a specific change in the DNA called a “nonsense mutation” which causes 10 to 15 percent of cases of Duchenne MD. Clinical trials have indicated that the drug may be able to slow down the progression of muscle weakness.

The next step will be for the European Commission to review this recommendation; the commission generally follows the advice of its advisers and a decision is usually handed down within three months.

Boris M Struk, Muscular Dystrophy Australia’s Executive Director, said:

“This recommendation by the EMA is great news – it gives us more confidence in the effectiveness and safety of Translarna as well as showing the willingness of regulatory authorities to give people with MD early access to new treatments. Translarna could potentially benefit the more than 100 boys and young men in Australia with Duchenne MD caused by a 'nonsense mutation'. The MDA will encourage government and regulatory bodies to act swiftly to ensure that the Australian MD community has unimpeded access to Translarna.”

What is a nonsense mutation?
A mutation is a change to the DNA code. Our DNA code is divided into genes which contain the instructions for the production of a particular protein and each gene has a start and a stop signal at the beginning and end. A nonsense mutation is when one letter of the DNA code within a gene is changed to another letter which unfortunately places a stop signal in the middle of the gene. As a result only part of the protein is made which is unable to perform its usual function. In the case of Duchenne MD no functional dystrophin protein is made. Dystrophin usually protects the muscles from damage and without it the muscles slowly deteriorate.

Ten to 15 percent of boys with Duchenne MD have a nonsense mutation. The most common type of mutation, which affects about two third of boys with Duchenne MD, is a “deletion mutation”. This means that large portions of genetic code (called exons which are numbered 1 to 79) are missing from the gene. About another ten percent of boys have what is called a “duplication mutation” where one or more exons appear twice within the gene. Clinical trials are underway to test exon skipping treatments for certain deletion mutations and utrophin up-regulation which is applicable to all mutations. For more information about all of the treatments being researched for Duchenne muscular dystrophy please read our factsheet (link in Further Information below).
How does Translarna work and how effective is it?
Translarna is an oral medicine that encourages the body to ignore stop signals in the middle of genes. So in Duchenne MD caused by a nonsense mutation, treatment with Translarna aims to increase the production of full length dystrophin protein which, if it reaches high enough levels can protect the muscles from damage. The drug is also being tested for other conditions such as cystic fibrosis.

The Phase 2b clinical trial indicated that Translarna increases dystrophin production and slows disease progression as measured by the 6-minute walk test. After 48 weeks of treatment boys taking the drug were able to walk 31.3 metres further on average than those taking placebo. It is important to note that the walking ability of those on the treatment still declined, but at a slower rate.

The safety results from the study showed that ataluren was well tolerated.

There was initially some confusion about the effectiveness of ataluren when the clinical trial results were first released in 2010 – it looked as if there had been no improvement in the treated boys. However, the trial included two different doses of ataluren and it turns out that, unexpectedly, the higher dose was ineffective. When only the lower dose results were analysed there was improvement in the 6 minute walk test as described above. The EMA also initially rejected the application for conditional approval for Translarna in January this year but on reassessing the data they came to this new decision.

What does conditional approval mean?
Conditional approval is granted to medicines that, based on available evidence, would give positive public health benefits which outweigh the risks. The available data about the safety and effectiveness of the medicine may not be comprehensive so the company is obliged, as part of the conditional approval, to carry out further clinical trials. The approval is renewed on a yearly basis until all obligations have been fulfilled, and is then converted from a conditional approval into a full approval. If further clinical trials give negative results, the medicine will be withdrawn from the market. Conditional approval can only be granted for medicines intended to be used for conditions that have no readily available treatment, and it is therefore important that patients have early access to the medicine.

Conditional approval means that PTC Therapeutics will be able to market Translarna in Europe (the 28 countries that are Member States of the European Union, as well as European Economic Area members Iceland, Liechtenstein and Norway) while it conducts its Phase 3 clinical trial, which is expected to complete enrolment by midyear and deliver results in 2015.

What does this mean for Australian’s with Duchenne MD?
Approval for Translarna in Australia will require a separate application to the Australian Therapeutic Goods Administration (TGA). Muscular Dystrophy Australia is currently consulting the TGA and PTC Therapeutics to find out more information about the steps that need to be taken to make Translarna available to Australian patients.
Boys with Duchenne MD between the ages of 7 and 16 who meet the eligibility criteria may be able to access the drug by enrolling in the phase 3 ataluren clinical trial – the Australian sites will be in Melbourne and Sydney.

What about Becker MD?
In very rare cases, nonsense mutations occurring in certain positions in the dystrophin gene can also cause the milder symptoms of Becker muscular dystrophy. It is anticipated that Translarna might also be able to help these rare patients.

Further information
- Read the full PTC Therapeutics Press Release
- Clinical trials - your questions answered
- More research news
- The MDA Duchenne and Becker MD factsheets contain more information about the condition including a research summary
- For definitions of any terms that you are not familiar with please take a look at our glossary
- Read about the research MDA funds which aims to reduce inflammation in the muscles and improve muscle regeneration
- You can get regular updates by becoming a friend of the MDA Facebook page or follow our Scientific Communications Officer on Twitter (@kelvidge).

If you have any questions, please contact us:

Email: Kristina.elvidgé@mda.org.au

Phone: (03) 9320 9555

Uploaded 27 May 2014