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Our reference
2020041787

Date 24 November 2020
Subject Advice on a potential candidate for conditional inclusion of ataluren (Translarna®) for Duchenne's muscular dystrophy (procedure: orphan drugs, conditionals and exceptionals)

Dear Mrs van Ark,

On 10 June 2020, the parties submitted an application for conditional inclusion in orphan drugs, conditionals and exceptionals to the National Health Care Institute for ataluren (Translarna®). Ataluren is registered for the treatment of Duchenne's muscular dystrophy due to a nonsense mutation in the dystrophin gene, in ambulatory patients aged two years and older. Based on the data in the dossier and the advice of the Scientific Advisory Board (WAR), I would like to inform you that the National Health Care Institute has concluded that treatment with ataluren in this group of patients with Duchenne's meets the criteria for conditional inclusion.

Application for conditional inclusion of ataluren
In its advice of 23 November 2017, the National Health Care Institute concluded that treatment with ataluren for Duchenne patients aged 5 years and older has a lesser value compared to placebo added to the best support care, due to insufficient evidence. A favourable effect of ataluren on slowing down the loss of walking capacity was not sufficiently demonstrated and the evidence for the mechanism of action of ataluren was not clear, as there was no pharmacodynamic confirmation. It was concluded that only a new study in a new selected sub-group can provide the necessary clarity.

Following this, an indication extension for children aged 2-5 years was submitted by the marketing authorisation holder (MAH) to the National Health Care Institute for the reassessment of ataluren. Since no new data had been published after the initial assessment of ataluren, this file was not accepted under the conditions for the submission of a reassessment. The new conditional inclusion of orphan drugs, conditionals and exceptionals started in August 2019.

We invited the relevant parties to submit an application (including a research proposal) for the conditional inclusion of the intervention in question.
On 10 June 2020, the parties submitted the dossier for conditional inclusion, including a research proposal.

Disorder and available effectiveness data
The application submitted relates to ataluren for the treatment of ambulatory patients with Duchenne's who are aged 2 years and older. Duchenne's is a relatively uncommon disorder. The application that has been submitted concerns a maximum of 16 patients who are eligible for treatment during the conditional inclusion process. Duchenne's is a serious, progressive and very rare genetic muscular disease that leads, among other things, to a rapid decline in physical functioning from early childhood. This progressive muscular disease is usually diagnosed before the child is 5. Most patients are wheelchair-bound before the age of 13. Up to approximately the age of 7, normal motor development can lead to an increase in motor functions in children with Duchenne's. On the basis of the research results of previous studies, there are indications that ataluren may result in a reduction in the patient's decline. There is currently no other treatment that affects disease progression in this group of patients.

Research proposal
The results of the registration studies with ataluren and natural progress data have led to an advancing understanding of Duchenne's disease progression. The disease can be distinguished in three phases: the stable phase, the mid-range phase and the rapid decline phase. In view of the course of the disease, it is expected that, mainly in mid-range patients, a clinically relevant effect on inhibiting the disease progression, loss of walking ability and physical functioning can be demonstrated. The applicants have submitted a research proposal for conditional inclusion, based on an ongoing international investigation, the 041 study. In this study, patients aged 5 years and older, who can walk at least 150 meters in 6 minutes, can participate. The primary objective of this study is to demonstrate the effectiveness of ataluren in mid-range patients aged 7-16 years. This study also looks at the broader ambulatory population, but this is not the primary objective of the study. In addition, the 025o-register study examines all ambulatory patients aged 2 years and older in the various stages of disease. The 045 and 046 studies look into the effect of ataluren on dystrophin production. For conditional inclusion, a Duchenne ataluren register is to be set up as part of the Dutch Dystrophinopathy Database (DDD) which is already managed by the Duchenne Centrum Nederland.

Advice of the Scientific Advisory Board on the quality of the research proposal
According to the WAR, the package question can be properly answered at the end of the conditional inclusion for the primary population analysis (mid-range patients) of the 041 study. However, there is more uncertainty about the population that is excluded here (rapidly deteriorating patients and stable patients). In order to extrapolate results from the proposed study to the entire ambulatory population at the end of the conditional inclusion period, the WAR members consider that at least the following is required:

- -A clinically relevant effect in the primary analysis population of the 041 study; and
- -More insight into the effect of ataluren on dystrophin production from the 045 and/or 046 study; and
- -At least confirmation should also be given for rapidly deteriorating patients and patients in the stable phase from the 041 and/or 025o study.

The WAR makes the following suggestions:

- •Establish a matrix for the current outcome measures that are perceived as the most important per age group and per disease phase (stable phase; mid-range phase; rapid deterioration phase)*;*
- •It is important to understand, during the course of the study, what is considered clinically relevant improvement in the stable and mid-range phase patients.

Assessment and conclusions of the National Health Care Institute

Based on the data in the dossier and the advice of the WAR, the National Health Care Institute has concluded that treatment with ataluren in this group of patients aged 2 years and older with ambulatory Duchenne's disease meets the criteria for CI[1], namely:

- •Ataluren has been granted marketing authorisation by the EMA and has 'orphan drug' and 'conditional' status;
- •This is a case of an unmet medical need;
- •The marketing authorisation holder is the dossier's lead applicant. The co-applicants are an independent research institute, attending physicians, and patient associations;
- •Based on the data it has collected, this study is expected to provide an answer to the question about inclusion in the Dutch insured package;
- •The National Health Care Institute anticipates that the question about inclusion in the Dutch insured package will be answered within 2.5 to 3 years.

The procedure for the conditional inclusion of orphan drugs conditionals and exceptionals indicates that entitlement to conditionally included care is linked to the requirement to participate in a study.
This means that patients are only entitled to reimbursement for care if they participate in the study into its effectiveness (or cost effectiveness). The Dutch Duchenne ataluren register is to be set up, because the current international main study is no longer accessible to Dutch patients.

Advice from National Health Care Institute

Based on these conclusions, we recommend that ataluren be designated as a potential candidate for conditional inclusion.

Phase 2 of the procedure will commence when you adopt this advice. We ask the parties to formulate their plans in greater detail and to draw up a covenant setting out the agreements needed to ensure that the CI process is conducted carefully and successfully. The Ministry of Health, Welfare and Sport will have to conclude a financial arrangement with the marketing authorisation holder. On the completion

[1] An overview of the criteria for CI can be found in the most recent version of the letter on the conditional inclusion procedure for orphan drugs, conditionals, and exceptionals. This letter can be found on our website, at: https://www.zorginstituutnederland.nl/werkagenda/voorwaardelijke-toelating-weesgeneesmiddelen-conditionals-en-exceptionals

of phase 2 (at which point a covenant will have been drawn up and a financial arrangement concluded), we will send you follow-up advice, on which you can base your final decision regarding the inclusion of ataluren in the conditional inclusion.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

cc The applicants (or co-applicants) who submitted the research proposal

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List 1. Price (Z-index) and dosage ataluren (Translarna®)

Ataluren is available in sachets of 125 mg, 250 mg and 1,000 mg granulate for oral suspension. The sachets of all different dosage strengths are packed per 30 sachets with a pharmacy purchase price of €3,072, €6,144 and €24,576 respectively. This means that ataluren costs €0.82 per mg. The dose is dependent on body weight, which means a different dosage for each patient. Ataluren is administered orally and no administration costs are expected.

Table 1. Pharmacy purchase price excl. VAT for ataluren (Translarna®) as of November 2020[2]

1 pack of 30 125 mg sachets	€3,072.00
1 pack of 30 250 mg sachets	€6,144.00
1 pack of 30 1000 mg sachets	€24,576.00
Calculated price per mg	€0.82

Ataluren should be administered orally three times a day.

The first dose must be taken in the morning, the second in the afternoon and the third in the evening. The recommended dosage intervals are six hours between the morning dose and the afternoon dose, six hours between the afternoon dose and the evening dose and twelve hours between the evening dose and the first dose the following day. The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight in the afternoon and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight).

Ataluren is available in sachets of 125 mg, 250 mg and 1,000 mg. The table below shows the sachet potency/potencies to be used during the build-up to the recommended dose based on body weight range.

Gewichtsbereik (kg)		Aantal sachets								
		Ochtend			Middag			Avond		
		125 mg sachets	250 mg sachets	1.000 mg sachets	125 mg sachets	250 mg sachets	1.000 mg sachets	125 mg sachets	250 mg sachets	1.000 mg sachets
12	14	1	0	0	1	0	0	0	1	0
15	16	1	0	0	1	0	0	1	1	0
17	20	0	1	0	0	1	0	0	1	0
21	23	0	1	0	0	1	0	1	1	0
24	26	0	1	0	0	1	0	0	2	0
27	31	0	1	0	0	1	0	1	2	0
32	35	1	1	0	1	1	0	1	2	0
36	39	1	1	0	1	1	0	0	3	0
40	44	1	1	0	1	1	0	1	3	0
45	46	0	2	0	0	2	0	1	3	0
47	55	0	2	0	0	2	0	0	0	1
56	62	0	2	0	0	2	0	0	1	1
63	69	0	3	0	0	3	0	0	1	1
70	78	0	3	0	0	3	0	0	2	1
79	86	0	3	0	0	3	0	0	3	1
87	93	0	0	1	0	0	1	0	3	1
94	105	0	0	1	0	0	1	0	0	2
106	111	0	0	1	0	0	1	0	1	2
112	118	0	1	1	0	1	1	0	1	2
119	125	0	1	1	0	1	1	0	2	2

The above information about the dosage of ataluren is taken from the SmPC[3]

[2] Z-index November 2020

[3] Source: Dutch SmPC ataluren (Translarna®) https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwie2PqGq_bsAhUpx4UKHbvmAQkQFjABegQIARAC&url=https%3A%2F%2Fwww.ema.europa.eu%2Fdocuments%2Fproduct-

The treatment of ataluren is stopped according to the criteria set out in the research proposal when the loss of ambulatory function occurs (loss of walking capacity). Loss of ambulatory function is defined as when the patient is no longer able to independently perform the 10-metre walking test as determined in the annual assessment by the physiotherapist. Contraindications may also be a reason to stop treatment.

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