EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 23 June 2011
2 EMA/CHMP/CNSWP/236981/2011
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on the need for a guideline on the 5 treatment of Duchenne and Becker muscular dystrophy

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Agreed by CNS Working Party	May 2011
Adoption by CHMP for release for consultation	23 June 2011
End of consultation (deadline for comments)	30 September 2011

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Comments should be provided using this template. The completed comments form should be sent to cnswpsecretariat@ema.europa.eu

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Keywords	*Concept Paper, Duchenne and Becker muscular dystrophy, Paediatric population, muscular biopsy, muscle strength, functional capacity, Orphan designation*

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1. Introduction

Neuromuscular diseases encompass a broad spectrum of diverse muscular disorders (e.g. inherited myopathies, metabolic and inflammatory myopathies), diseases of neuromuscular transmission (e.g. myasthenia gravis, Lambert-Eaton myasthenic syndrome, hereditary neuromuscular disorders) as well as disorders of the upper and lower motoneurons (e.g. amyotrophic lateral sclerosis, spinal muscular atrophy). Neuromuscular diseases can involve both, muscles that are moved voluntarily and those that function automatically, e.g. for breathing. Patients suffering from neuromuscular diseases experience a loss of muscle control, strength and function, which is either due to primary muscular damage or to secondary muscular atrophy resulting from neuronal understimulation. A significant part of the patients with these disorders suffer from fatal conditions with reduced life expectancy.

Treatment of neuromuscular diseases should alleviate symptoms, delay or stabilize disability progression (disease modifying effect) and improve quality of life as well as long-term survival of the patients. So far, only limited treatment options exist for these rare but severe diseases. Medicines that are currently used for the treatment of neuromuscular disorders include amongst others various immunotherapeutic drugs for e.g. inflammatory myopathies, although due to the lack of controlled trials and standardized outcome parameters, their use is still considered empirical [1], as well as corticosteroids, which represent the gold standard of treatment in Duchenne muscular dystrophy (DMD), although no consensus exists regarding the best treatment scheme [2].

The large variety of neuromuscular disorders provides a high variability, e.g. with regard to disease onset and clinical symptoms, that may request specific treatment approaches as well as different study designs and outcome parameters. For the moment the scope is therefore limited to Duchenne (DMD), the most common and severe form of muscular dystrophy [3], and Becker (BMD) muscular dystrophy. An addendum could be added later as needed, where similar neuromuscular diseases are going to be grouped together and existing guidelines are reviewed.

2. Problem statement

Recent advances in basic and clinical research have opened new perspectives for future therapeutic options [4]. Regarding the role of molecular diagnosis in myopathies [5], a tremendous increase of data on numerous hereditary myopathies was seen during the last couple of years, showing that the clinical diagnosis can be supplemented by morphological and protein expression data from muscle biopsy samples. In parts of these disorders as in DMD and BMD the diagnosis can be confirmed by genetic testing (e.g. mutation detection in the related disease gene).

At present various potential approaches are under development for the treatment of neuromuscular disorders. With regard to Duchenne muscular dystrophy, the development includes agents that enhance dystrophin expression, hopefully delay muscle dystrophy, modulate inflammatory responses [3] and improve muscle function. The increasing number of clinical trials that court a rather small number of patients have raised several issues, including the study design, the choice of appropriate efficacy endpoints in general and of reliable surrogate outcome measures in clinical multicenter trials [3, 6] and the duration of the trials (long-term treatment goals [7]). Many new assessment tools, that can be used as outcome measures for muscle strength [8], motor function[9], quality of life or the evaluation of cardiac and respiratory function are validated or under validation. As Duchenne/Becker muscular dystrophy have an onset in earliest childhood but also cover a broader age spectrum, specific difficulties have been identified that pertain to diagnostic criteria, age-related clinical relevance [10] and different safety.

Both, DMD and BMD are rare diseases, DMD is additionally life-threatening. One out of 3500 boys worldwide is born with a mutation in the gene for dystrophin.[3] Thus, some of the therapeutic interventions might qualify for orphan designation through the Committee for Orphan Medicinal Products (COMP) which should be considered in the preparation of the guideline.

3. Discussion (on the problem statement)

In the proposed update of the guidance document, the following issues will be discussed:

Choice of patient population

- Paediatric population to be the central target population as both diseases have an early onset and are diagnosed during childhood
- Reliable diagnostic criteria, including genetic verification, muscle biopsy data [11] and imaging modalities
- Thresholds for clinical severity of muscle function impairment, cardiac und pulmonary symptoms and associated cognitive deficits

Study design

- Need and kind of pharmacodynamic studies including biomarkers as surrogate endpoints
- Definition of primary and relevant secondary endpoints:
  - Choice of age-related endpoints and clinically relevant improvement
  - Surrogate endpoints that could be used for isometric and dynamic muscle strength, generic [9] or specific disease global motor function tests, timed activities, cardiac and pulmonary function [6]
- Need for and choice of comparator groups (active comparator and/or placebo)
- Duration of efficacy studies
- Usefulness of combination therapy and corresponding study designs
- Generalisability of data with respect to different age groups
- Need for long-term maintenance of efficacy and safety data

4. Recommendation

To ensure uniformity of clinical studies and to set standards, the Working Party/Committee recommends drafting a guideline on the treatment of Duchenne and Becker muscular dystrophy.

5. Proposed timetable

It is planned to publish a draft revised guideline no later than Q2 2012. The draft revised guideline will be available for 6-month consultation before its finalisation.

6. Resource requirements for preparation

The preparation of this guideline will involve mainly the CNSWP, PDCO, BSWP and COMP.

7. Impact assessment (anticipated)

It is aimed that the Guideline on the treatment of Duchenne and Becker muscular dystrophy will be helpful to achieve consensus in the evaluation of such products by regulatory authorities in the European Community. Furthermore, it is expected, that such guidance document would improve quality and comparability of development programs for this indication by pharmaceutical companies.

8. Interested parties

European Alliance of Neuromuscular Disorders Associations (EAMDA)

European society for Muscle Research

Translational Research in Europe – Assessment and Treatment of NeuroMuscular Disease (TREAT-NMD)

9. References to literature, guidelines, etc.

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