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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

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This guideline replaces NfG on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (CPMP/EWP/561/98)

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Guideline is intended to provide guidance for the evaluation of drugs for the treatment of multiple sclerosis. It should be read in conjunction with the Directive 75/318/EEC, as amended, and other current and future CHMP and ICH guidelines, in particular the guidelines on:

- Statistical principles for clinical trials (ICH topic E9)
- The extent of population exposure to assess clinical safety (ICH topic E1)
- Pharmacokinetic studies in man
- Dose response information to support drug registration (ICH topic E4)
- Investigation of drug interactions
- Choice of control group in clinical trials (ICH topic E 10)

1. INTRODUCTION (background)

Multiple Sclerosis (MS) is a common neurological disease affecting more than 1 million people worldwide. Its prevalence rate varies between races and geographical latitude, ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe.

MS is an inflammatory condition that damages the myelin of the Central Nervous System and causes neurologic impairment and, frequently, severe disability. It is the commonest cause of neurological disability in young and middle-aged adults and has a major physical, psychological, social and financial impact on patients and their families, friends and bodies responsible for health care.

The aetiology of MS remains unknown. It is generally assumed that MS is mediated by some kind of autoimmune process possibly triggered by infection and superimposed upon a genetic predisposition. As many as 80 to 85 % of all patients present with a form of disease known as relapsing-remitting MS (RRMS), which is characterised by unpredictable acute episodes of neurological dysfunction named clinical attacks or relapses, followed by variable recovery and periods of clinical stability. Within ten years more than 50% of patients who presented with a RR form eventually develop sustained deterioration with or without relapses superimposed; this form is called the secondary progressive variety of MS (SPMS). The term relapsing MS (RMS) applies to those patients either with a RRMS form or a SPMS form that are suffering relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatments. Around 15% of patients develop a sustained deterioration of their neurological function from the beginning; this form is called primary progressive MS (PPMS). Some patients who begin with a progressive deterioration may experience relapses with time and this form is called progressive relapsing MS (PRMS). Besides these main types of disease, the benign variety of MS refers to a RRMS form with few relapses and no significant disability after several years of evolution. Conversely, the term malignant MS applies to a very aggressive variety leading to severe disability or death in a few years after the onset of the disease.

Finally, the term clinically isolated syndrome (CIS) applies to those patients who have suffered a single clinical event but do not comply with the diagnostic criteria for definite MS.

It is unclear whether the different courses of MS described are due to the same or to distinct pathophysiologic processes. Relapses are considered the clinical expression of acute inflammatory focal lesions whereas progression is considered to reflect the occurrence of demyelination, axonal loss and gliosis. Relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis are probably different stages of the same disease while primary progressive multiple sclerosis may imply different processes.

In general, current therapeutic approaches include:

Symptomatic treatment. This refers to all therapies applied to improve symptoms caused by the disease: fatigue, spasticity, ataxia, weakness, bladder and bowel disturbances, sexual dysfunction, pain, tremor, paroxysmal manifestations, visual impairment, psychological problems, cognitive dysfunction and other associated conditions that can improve with non specific treatments. Clinical development of these products is out of the scope of this guidance.

Treatment of acute relapses with corticosteroids

Treatment aimed to modify the course of the disease. In this category there are therapies aimed to decrease the relapse rate or modify relapses; therapies aimed to diminish the accumulation of disability in time; and future therapies that pursue neuroprotection or intend to restore neurological function (e.g. by means of promotion of remyelination).

Recent studies suggested that progression of lesions in MS might have, even in early clinical stages, two components: an active immunological aspect and a degenerative aspect; it is unknown to what extent these are causally interrelated. Currently approved therapies to modify the MS course target the immunological processes of the disease. Most of them are considered to act as immunomodulators but their mechanisms of action have not been completely elucidated: the relationships between changes of the immune response induced by these agents and the clinical efficacy in MS is far from settled. Immunosupressants or cytotoxic agents are also used in some patients after failure of conventional therapies.

Based on the immunological nature of the disease, combination therapy targeting different parts of the immune processes may be reasonable and development of a new treatment as a combination therapy is a possible strategy.

2. SPECIFIC CONSIDERATIONS WHEN DEVELOPING PRODUCTS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

2.1 Different goals of treatments

Treatments of MS may have different goals that will lead to different clinical development plans and clinical trial designs:

A) Treatment of acute relapses to shorten their duration and/or severity of symptoms and/or preventing their sequelae.

B) Modification of the natural history of the disease. This includes:

- Preventing or delaying the accumulation of disability. This may refer to the sustained accumulation of disability related with relapses or to the progression of disability either in the progressive phase of the disease (SPMS) or in PPMS. Those three situations demand a separate approach.
- Preventing or modifying relapses. It is not clear to what extent the effect on relapses is related to the prevention or delay in the long-term accumulation of disability, which is considered a more clinically relevant effect

C) Improvement of an apparently stable residual disability

2.2 Treatments for acute relapses

Neurological impairment due to a relapse may improve spontaneously within weeks or few months. However, regarding a specific attack, prediction of the course and degree of later functional recovery is not possible. Therefore, parallel controlled clinical trials are mandatory to assess the benefit of any new therapy.

Corticosteroids are the accepted treatment for acute relapses in MS. Plasmapheresis is used in severe relapses based on limited data. Corticosteroid therapy shortens the duration of the relapse and accelerates recovery, but there is no evidence that corticosteroid treatment improves the overall degree of recovery or alters the long-term course of the disease. These are relevant issues when investigating new treatments for relapses.

As there is no agreement about the specific criteria of corticosteroid treatment (e.g. dosage, method of administration, tapering,..) the actually chosen regimen should be stated and justified in the protocol.

If, for a test drug only an effect on the duration, severity and/or recovery from a relapse is claimed, this claim should be based on clinical trials with corticosteroid treatment as positive control and a placebo arm for the internal validation of the study. Even if only relapses with homogeneous signs or symptoms are considered, it is recognised that it is difficult to give a reliable assessment of the

severity of a relapse, either using clinical judgement or neurological scales. MRI with gadolinium may inform on the duration of the inflammatory activity.

The trial should include escape conditions to allow switching to standard therapy when the patient fails to improve or even worsens. Patients should be followed for an appropriate time (e.g. at least 6 months) after each relapse to be sure that the degree of recovery after the relapse is well assessed. It is recommended also to investigate the modification of the subsequent clinical course of the disease in terms of time free from subsequent relapse and progression of disability. The investigation of a modifying the effect on other products being used concomitantly as chronic treatments intended to modify the natural course of the disease, may be also valuable.

If an effect is claimed with regard to the degree of recovery after a relapse and/or the long-term course of the disease, this should be demonstrated by means of placebo-controlled superiority trials.

2.3 Treatments intended to modify the natural course of the disease

It is important to differentiate between the clinical patterns of the disease: RRMS, SPMS with and without relapsing activity and PPMS (see 1.). Although these patterns are defined according to clinical features (occurrence of relapses, presence of gradual progression of disability) differences in histopathology and MRI (Magnetic Resonance Imaging) activity are also present.

2.3.1 Relapsing multiple sclerosis

The term relapsing MS includes 1) patients with RRMS, 2) patients with SPMS and superimposed relapses and 3) patients with a single demyelinating clinical event who show lesion dissemination on subsequent MRI scans according to McDonald's criteria.

Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability as sequelae of acute relapses, are meaningful goals in the treatment of RMS

Progression of disability, as a result of relapses from which patients do not fully recover take many years and, for the moment, there are no surrogate variables for evaluating progression of disability. Therefore large-scale long-term parallel group trials are required to establish clinically relevant treatment differences on disease progression.

Relapse rate, relapse duration, recovery after relapses are all highly variable between patients and within one patient. Therefore, treatments intended to decrease the relapse rate or modify relapses should be evaluated in parallel trials sufficiently large and long to overcome this inter and intra-individual variability.

Currently approved therapies have demonstrated a favourable effect on the rate and severity of relapses and some products also in the short-term (a few years) progression of disability. If a product demonstrates a benefit in relapse rate or severity without an accompanying effect on preventing or delaying disability, the clinical relevance of such benefit should be justified. For this reason studies aimed to evaluate an effect on relapse rate should also generate data with respect to disability.

Although the effect on relapse rate may be investigated in patients with any form of relapsing MS, it is advisable to assess the effect on disability only in patients with relapsing remitting MS. It is therefore accepted that the indication in relapsing MS will mainly rely on the effects shown in patients with relapsing remitting MS and that an effect on relapses in relapsing remitting MS may be extrapolated to an effect on relapses in secondary progressive MS.

Several major placebo-controlled clinical trials have provided evidence of an apparent short-term stabilisation in placebo-treated patients that could be explained, among others, by the regression to the mean phenomenon, and by a real placebo effect, as well as by the natural course of the disease. Approved therapies have been shown to favourably modify the short-term evolution of the disease although the benefit is modest, at the cost of significant inconveniences and side effects and it is not known whether the effect is maintained for years. Differences from placebo are not consistent across trials and the sensitivity of the available scales to measure progression of disability as well as other characteristics of clinical trials in this field do not assure the ability to detect clinically relevant differences.

Therefore, equivalence (non-inferiority) trials are insufficient, as the only proof of efficacy and demonstration of superiority against placebo or active comparator should be provided.

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