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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT AND PREVENTION OF BIPOLAR DISORDER

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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICAL PRODUCTS IN THE TREATMENT AND PREVENTION OF BIPOLAR DISORDER

These notes are intended to provide guidance for the evaluation of medicinal products in the treatment of bipolar disorder. They should be read in conjunction with the Directive 75/318/EEC, as amended, and other pertinent elements outlined in current and future EU and ICH guidelines, especially those on:

- Pharmacokinetic studies in man
- The extent of population exposure to assess clinical safety for drugs intended for long-term treatment in non-life threatening conditions (ICH topic E1)
- Statistical principals for clinical trials (ICH topic E9)
- Studies in support of special populations: Geriatric (ICH topic E7)

They are intended to assist applicants in the interpretation with respect to specific problems presented by compounds in the treatment of acute manic episode and the prevention of recurrent episodes in bipolar disorders ("mood stabiliser").

Note: See for the depressive phase of bipolar disorder the antidepressant guideline and the relevant section in this document.

1. INTRODUCTION

Bipolar disorder is in general a chronic disease. In DSM IV a distinction is made between Bipolar I disorder, Bipolar II disorder, Cyclothymic disorder and Bipolar disorder NOS (Bipolar disorder NOS will not be discussed in this paper).

Bipolar I disorder: At least one Manic episode or mixed episode. Often individuals have also had one or more Major depressive episodes. (see for criteria Manic Episode DSM IV)

Bipolar II disorder: At least one Major Depressive episode accompanied by at least one hypomanic episode (see for criteria Hypomanic Episode DSM IV)

Although a heterogeneous group of patients is covered by these disorders, the personal tragedy associated with these disorders is extreme. Especially the manic episode can cause marked impairment in occupational functioning or in usual social activities or relationships. Also depressive episodes can cause marked impairment.

The worldwide lifetime prevalence of bipolar I disorder is about 0.4% to 1.6% and of bipolar II disorder about 0.5%. The onset of the disorder occurs relatively early in life, and most patients have long-lasting disorder.

The development of effective approaches to the treatment of bipolar disorder requires an accurate method of diagnosis. The current diagnostic criteria are made explicit in the *Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM IV*) and in the *International Classification of Diseases, Injuries and Causes of Death (ICD 10*). These criteria are valid for the purpose of case identification.

Currently available treatments are the following:

Lithium is licensed in most countries for the *indication* "*prevention of recurrent episodes in manic-depressive disorder*" as well as for "*prevention of recurrent depressive episodes*" and "*treatment of mania*".

In some countries carbamazepine is approved for prophylaxis of manic-depressive illness unresponsive to lithium and divalproex for manic episodes associated with bipolar disorder.

In Europe, neuroleptics and benzodiazepines are commonly used for acute management of mania. Treatment with these compounds is often short-time and during this period usually treatment with a product like lithium is started. However actual treatment may differ between treatment centres due to regulatory status or treatment habits.

In this paper a distinction is made between the treatment of acute manic episode of bipolar disorder and the prevention of bipolar disorder.

Major depressive episode in the framework of bipolar disorder might be considered as a separate indication. See the antidepressant guideline for the requirements of trials in major depressive episode.

2. DEFINITIONS

2.1.1 Maintenance of effect: the effect of treatment, seen in the short-term studies is maintained during the whole (hypo) manic episode. In the literature this treatment phase sometimes is called the continuation period.

2.1.2 Relapse: Relapse is defined as an increase in symptomatology immediately or almost immediately after medication is stopped, i.e. during the index episode.

2.1.3 Recurrence: is defined as a re-emergence of symptoms (new episode) after a time with no or minimal symptoms.

2.1.4 Response: clinically relevant improvement (**Note:** This must be defined in advance of the study).

2.1.5 Responder: patient with clinically relevant predefined improvement.

2.1.6 Remission; Remission is defined as a condition where no or only few signs of illness remain. Recovery is a sustained period of remission representing resolution of the index episode.

3. EFFICACY CRITERIA

For the indication bipolar disorder, the effect of a product in both the acute phase and in prevention of further episodes should be shown, but actual development of a product may differ, depending on the mechanism of action and the perceived usefulness in the treatment spectrum of comparable agents e.g. classic neuroleptics in acute mania. Specific indications could be acceptable when justified. However, even if a product is only effective in one situation (e.g. treatment of acute manic episode) it is important to know whether it affects another situation of bipolar disorder (e.g. induce switch from mania to depression), so that longer term or maintenance data are also considered necessary in case of mere “acute treatment” claims.

In other words a product may be developed for the indication bipolar disorder, which includes both treatment of manic episodes/depressive and prevention of further manic/depressive episodes

A licence may also be considered for the treatment of manic episode and prevention of manic/depressive episodes separately:

As episodes of Major Depression may occur in the framework of bipolar disorder and even may be the more important issue e.g. in bipolar II, the effect of a new product meant for bipolar disorder or for prevention of manic/depressive episodes, may be studied in this situation. It is sometimes called “bipolar depression”.

Use in other situations like rapid cycling or mixed type patients might be considered too.

3.1 Indication "bipolar disorder"

Though a diagnosis of Bipolar Disorder might be based on episodes of mania alone, usually patients will have both episodes of mania and major depression during their live. Therefore, to obtain this claim a compound should show efficacy in the treatment of manic episodes (see section 3.2), episodes of Major Depression (see section 3.4) and prevention of manic/depressive episodes (see section 3.3).

It is expected that generally a product will be developed in bipolar I disorder. If specifically the indication bipolar II is sought, efficacy should be shown in patients with a hypomanic episode and prevention of (hypo) manic/depressive episodes.

Evidence of efficacy in an episode of mania allows extrapolation to hypomania, but not the other way around.

3.2 Indication " treatment of manic episode"

Efficacy has to be demonstrated in short-term studies showing an effect in manic episode; in addition it should be shown that efficacy is to be maintained during the episode.

To study the product in combination is of importance too (see section 6.1)

The occurrence of switching to depression should also be investigated.

For specific claims (e.g. or "with psychotic features") additional studies are necessary.

3.3 Indication "recurrence prevention"

Efficacy has to be demonstrated in long-term prophylactic treatment studies with the purpose of preventing recurrence of (hypo)manic/depressive symptoms (new episodes)

3.4 Indication "major depressive episode in the framework of bipolar disorder"

To obtain this claim a compound should show efficacy in "bipolar depression". Results from studies with antidepressants in unipolar depression may be partly extrapolated to "bipolar depression". However, results from studies in "bipolar depression" (e.g. atypical neuroleptics, mood stabilisers) cannot be extrapolated to the unipolar situation.

3.5 Indication "rapid cycling" or other situations

A claim for a specific situation, such as treatment of rapid cycling patients or mixed type, has to be supported by specific studies. For other specific situations like therapy resistant patients data are lacking to enable a well-documented advice.

Data from rapid cyclers cannot be extrapolated to the whole group of patients with bipolar disorder.

4. METHODS TO ASSESS EFFICACY

Efficacy should be assessed by means of rating scales. The choice of instruments (rating scales) should be justified from the test quality criteria (reliability, validity and sensitive for change). For the assessment of improvement specific developed rating instruments are necessary. In addition global assessment is needed.

4.1 Manic episode

The Manic State Rating Scale and the Young Mania Rating Scale are measurements with well-known reliability and validity. The Bech-Rafaelsen Mania Scale (BRMAS) is a

European scale that is not widely used but is reliable and valid. These rating scales can be used for assessing improvement in manic episode and maintenance studies.

Furthermore a global scale may be used as secondary endpoint. Although such a scale is generally not very sensitive for change the magnitude of the effect seen on such a scale gives an impression of the clinical relevance of the effect seen on the specific scales used.

The use of lifecharting may also be used as a secondary endpoint.

Reliable depression scale (e.g. Hamilton Depression Rating Scale, Montgomery, Åsberg Rating Scale, Bech-Rafaelsen Depression Scale) should be used to assess switching from mania to depression.

Improvement on the symptomatology should be documented as the difference between baseline and post-treatment score and should also be assessed with respect to response criteria; for example the proportion of patients with a certain % of improvement, depending on the kind of patients included. At present, response criteria are not well defined and it is unknown how much improvement should be considered as a clinically relevant improvement. Manic episodes in general show a quicker and more pronounced response to therapy than depression or schizophrenia. Therefore, the response criteria could probably be more stringent than the ones currently used for depression and schizophrenia. In any case the criteria for response should be justified by the company in advance of the study. Choice of endpoints should be indicated and the clinical relevance of expected effects should be defined by the degree of symptom reduction and discussed in the protocol with reference to other comparable data or publications available. In 12-week studies % remitters might be a more relevant endpoint than responders.

In acute manic patients, onset of action and time to response is an important parameter and should be investigated.

4.2 Recurrence prevention

Both the proportion of patients developing mania or depression over time and time to either event are of importance to describe the effect of a product in prevention of recurrence. Both should be available in the statistical analysis. The number of patients should be sufficient to address both recurrences of depression and of mania. Researchers should use the same scales to document recurrence as they have used in the acute studies.

Criteria for stabilisation, prodromal signs and recurrence of both (hypo)manic symptoms and depressive symptoms should be defined in advance of the study and have to be discussed in the protocol with reference to other comparative data or publications available. Usually a recurrence includes the reappearance of manic or depressive symptoms, scored on a validated scale during one or more visits.

4.3 Major depressive episode in the framework of bipolar disorder

The conventional depression scales (used in unipolar depression) like the Hamilton depression rating scale or the Montgomery-Asberg depression rating scale are acceptable. See also the guideline for depression.

4.4 Indication “rapid cycling”

The scales mentioned in the above are acceptable.

Data are lacking to give further advice, but, as rapid cycling is defined as 4 or more cycles per year, it might be considered to define efficacy by a clinically relevant reduction of cycles.

5. STUDY POPULATION AND SELECTION OF PATIENTS

The disorders should be classified according to an internationally acknowledged classification system, preferably DSM IV , using the diagnostic criteria given herein. A rating score alone is insufficient and is not equivalent to a diagnosis. Moreover patients should also be classified according the severity score. Furthermore detailed history (duration of bipolar disorder, duration of present episode, number of exacerbations, as well as previous treatment outcome) should be documented.

In addition cut-off scores, based on appropriate scales should be used as inclusion criteria. It is essential that the inclusion criteria and reason for treatment with a pharmacological agent should be perfectly clear to the reader of the study report.

5.1 Manic episode

In short term trials to assess the effect on mania, preferably patients with only an episode of mania should be included.

5.2 Prevention of manic/depressive episode

Patients with bipolar I disorder that are in full remission should be included in the study. To demonstrate recurrence prevention it is recommended to include patients with a reasonably high recurrence rate only. However patients included should be free of manic/depressive symptoms for a sustained period of time at the start of the study so that if manic or depressive symptoms occur, recurrence can be distinguished from relapse.

5.3 Major depressive episode in bipolar disorder

Both bipolar I and bipolar II patients might be included and the possibility of further subgroup analysis might be allowed if justified in the protocol.

Patients should be diagnosed as having Major Depressive episode as part of a bipolar disorder as defined by usual criteria e.g., DSM IV.

6. STUDY DESIGN

To assess the effect of medicinal products parallel controlled trials are necessary. Efficacy should be studied using trials with active and placebo controls. The active treatment should be a standard product in an adequate dosage.

The sample size should be justified and should be estimated preferably on responders (see section 2). Statistical analysis should include various analyses, among others intention-to-treat and per protocol. The handling of dropouts and missing data should be prospectively planned in the trial protocol. The risk of under- or overestimation of the effect should be addressed. See further the biostatistical guideline.

Investigators should be properly trained in evaluating the patient. Inter-rater reliability scores (kappa) should be documented for each investigator in advance and during the study, both with regard to the diagnosis and to rating scales used for efficacy and/or safety, where relevant.

When concomitant medication is allowed that could affect outcome, it should be documented in detail and its impact on efficacy should be evaluated

Prior medication and “other” concomitant medication have to be documented in detail. Relevant medication has to be washed out. If appropriate, rescue medication should be provided.

Drop-outs and reasons for drop-out have to be documented in detail. Moreover information concerning time to drop out should be provided. In addition information of patients screened but not included in the study should be documented.

Standardised psychotherapy, psycho-education, support or counselling may be given as supplementary treatment, but should be standardised, documented and taken into account when analysing the results. The possibility of centre effects has to be evaluated carefully.

As compliance is a problem in these patients, compliance controls and screenings for additional illicit psychotropic substances are recommended.

6.1 Acute manic episode

Preferably, patients should be off medication with anti-manic properties. Ideally, patients need to be off lithium or mood stabilisers at baseline for a substantial period of time because of possible rebound phenomena. Moreover, they should not be lithium resistant (acute manic episode under lithium therapy) as this has consequences for the claim requested.

Patients should preferably start the treatment on a more or less stable symptom baseline, and any reason to exclude placebo-responders should be discussed. Generally a placebo wash-out period to exclude placebo responders is not useful and may impair generalisation of the results.

Efficacy has to be shown in preferably 3-arm studies with a duration of 3-4 weeks. Frequent assessments will be necessary if the onset of action is evaluated. In addition, as maintenance of effect during the episode has to be shown, efficacy has to be demonstrated during 12 weeks. A placebo control during this period will be difficult. Therefore an active comparator is acceptable, provided that assay sensitivity is taken into account. A possible design is a comparison of placebo, test product and active control for three weeks followed by a two-arm phase for the remaining nine weeks, comparing only test product and active control. At least 2 assessment time-points are used in this study; one at 3 weeks, comparing the results of active comparator and test product with placebo and one at 12 weeks comparing the results of active comparator and test product. The choice of comparator will depend on the product to be investigated and should be justified.

In a manic episode treatment of antipsychotic compounds and “mood stabiliser” is usually combined or treatment is started with the one and the other is phased in. Together with the placebo-controlled study mentioned in the above clinical efficacy and safety of the new product also has to be studied in the clinical situation of add on therapy e.g. by comparing the new compound, the suitable additional compound and the combination of both during 6-12 weeks.

The occurrence of switching to depression should also be investigated. Criteria for “ switching” (e.g. change in symptoms) have to be defined in advance of the studies.

For specific claims (e.g. or “with psychotic features”) additional studies are necessary.

6.2 Prevention of manic/depressive episode

Long-term trials are needed versus placebo and/or suitable comparator e.g. lithium. The choice of comparator has to be clearly justified and the risks should be carefully considered.

The duration of the study should be long enough to demonstrate recurrence prevention. (See 7.2.2.2)

6.3 Major Depressive episode in the framework of bipolar disorder

Study drugs may be used as monotherapy, or in combination. However, this has consequences for the claim. For a monotherapy claim, patients need to be off lithium or other mood

stabilisers at baseline for a substantial period of time because of possible rebound phenomena. Moreover, they should not be lithium resistant (depression under lithium therapy) as this has consequences for the claim requested.

Before licensing, studies in both unipolar and bipolar depression should be conducted. A positive result in both would strengthen the result in bipolar alone, whereas a negative result in unipolar depression has consequences for the SPC.

Studies of the acute phase should be of 6-8 weeks duration.

Three-arm trials including both a placebo and an active control are recommended.
The choice of the active comparator needs to be justified.

Showing maintenance of effect in bipolar depression - as in major depression- is needed; 3-6 months should be sufficient.

Switching to hypomania or mania is thought to be an important safety issue. Switching criteria need to be defined so that not only full blow mania is considered. Incidence of switching needs to be established in relation to comparator as well as placebo.

For the requirements of trials in major depression see also the depression guideline.

6.4 Specific groups

Geriatric patients

Bipolar disorder is not typical for elderly people. Therefore, no special studies in the elderly are necessary for the indication manic episode and prevention of manic/depressive episode.

Safety might be a concern, as for other centrally active products. Information for this group concerning the effective and safe dose is necessary (ICH E7). When indicated, this has to be investigated.

Children and adolescents

Bipolar disorder develops in early adulthood. Therefore, in younger children specific studies do not seem to be relevant. In adolescents efficacy and safety evaluation is highly desirable.

7. STRATEGY

7.1 Clinical-pharmacological studies

7.1.1 Pharmacodynamics

A variety of tests can be performed but there is no specific model for manic episode/bipolar disorder. Studies in cognition, reaction time etceteras may be necessary depending on the side effect pattern of the product (see section 8).

7.1.2 Pharmacokinetics

No specific requirements for medicinal products in manic episode/bipolar disorder are necessary (see Guideline on Pharmacokinetic studies in man).

7.1.3 Interactions

The need for interaction studies depends on the metabolism of the new product (see guideline on Interactions).

Pharmcodynamic interactions with alcohol and other CNS-active products should be investigated.

7.2 Therapeutic studies

7.2.1 Initial therapeutic studies

7.2.1.1 Manic episode

The purpose of this phase of investigation is to

- identify patients who may benefit from the medicinal product
- obtain initial information on safety
- establish suitable therapeutic dose ranges and frequency of dosing

Dose ranging studies might be performed in a controlled, titration and/or fixed dose design, using at least 3 dosages, to establish the lower end of the clinical effective dose range as well as the optimal dose. Determination of drug concentration in plasma may be useful.

7.2.1.2 Prevention of manic/depressive episode

The usefulness of including more than one dose of the new compound to investigate the optimal dose for long-term treatment should be considered.

7.2.2 Main therapeutic studies

7.2.2.1 For the indication manic episode

See section 6.1. To prove efficacy in manic episode the choice of active comparator is of importance.

7.2.2.2 Prevention of manic/depressive episode

Controlled studies against placebo and reference therapy (3-way studies) are first choice. In this way both the effect of the new compound can be shown and the relative benefit /risk can be assessed. If only an active comparator is used, assay sensitivity should be addressed adequately. Due to the changing course of bipolar disorder and the chronic character with recurrences of depressive and (hypo)manic symptoms studies with a long duration (at least one year) are necessary.

8. SAFETY ASPECTS

Identified ADRs should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and cardiological recordings. Specific rating scales are preferred where relevant.

Compliance should be monitored with pill counts and interviews as well as pharmacokinetically, and reports on clinical trials should assess compliance statistically.

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug reactions, drop-outs and patients who died while on therapy. Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided. Special efforts should be made to assess potential adverse effect reactions that are characteristics of the class of drugs being investigated depending on the action on various receptor sites (direct questioning by investigator). Particular attention should be paid to anti-dopaminergic, anti-cholinergic, anti-histaminergic, serotonergic, α-adrenergic, GABA system mediated side effects:

Special attention should be paid to switching events.

8.1 Neurological adverse reactions

Depending of the product extrapyramidal side-effects (EPS) should be diagnostically classified and followed specially with specific designed rating-scales. Any claims should be substantiated by comparison with at least one active control preferably in two doses (at least one (effective) dose should be relative low exhibiting rather low EPS). The choice of the comparator and the dose(s) should be justified.

Tardive Dyskinesia (TD) is a side effect that generally occurs late in the treatment of antipsychotics. The possibility should be mentioned in the SPC. Specific claims have to be substantiated using the same conditions as for EPS. The duration of treatment has to be justified.

Confusion, stupor lethargy and coma should be documented.

Neuroleptic malignant syndrome is of specific concern and diagnosis and management of this condition during the trial should be specified and patients followed up until the outcome is clear.

Seizures should be documented.

During the wash-out phase, an attempt should be made to distinguish between pre-existing acute and/or tardive EPS.

8.2 Psychiatric adverse reactions

Depending on the class and the interactions with various receptors effects on cognition, reaction time and/or driving and the extent of sedation should be studied. Specific claims always have to be based on specific studies.

8.3 Cardiovascular adverse reactions

Special attention should be paid to arrhythmia and conduction disorders, in particular QT-interval prolongation and dispersion in a class associated with cardiovascular effects.

8.4 Haematological adverse reactions

Especially attention should be paid to agranulocytosis and aplastic anaemia and reduction in platelet count.

8.5 Endocrinological adverse reactions

Special attention should be paid to sexualdisturbances, galactorrhea, gynecomastia and weight gain.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of neuroendocrinological parameters (e.g. prolactin) may be necessary.

8.6 Gastro-intestinal adverse reactions

Special attention should be paid on nausea, vomiting and diarrhoea.

8.7 Urinary tract adverse reactions

Special attention should be paid to urinary frequency, thirst and renal function disorders.

8.8 Other adverse reactions

Other adverse reactions, e.g., alopecia, twitching, hepatic function, thyroid dysfunction, or hyperammoaemia, might occur and should be documented.