MEDICINAL PRODUCTS FOR THE TREATMENT OF DEPRESSION

Guideline Title: Medicinal Products for the Treatment of Depression
Legislative basis: Directive 75/318/EEC as amended
Date of first adoption: February 1990
Date of entry into force: August 1990
Status: Last revised February 1990
Previous titles/other references: Anti-Depressant Medicinal Products
Additional Notes: This note for guidance is intended to assist applicants for a marketing authorisation in the interpretation of Directive 75/318/EEC as amended with respect to specific problems presented by clinical investigations of medicinal products intended to be used for treating depression. This version replaces the 1988 guideline: Anti-Depressant Medicinal Products.

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MEDICINAL PRODUCTS FOR THE TREATMENT OF DEPRESSION

This note for guidance should be read in conjunction with Part 4 of the Annex to Directive 75/318/EEC, as amended; it is intended to assist applicants in the application of this Directive with respect to specific problems presented by clinical investigations of medicinal products intended to be used for treating depression.

1 FIELDS OF APPLICATION

11 General goal

The general goal of antidepressant medicinal products is to treat depressive illness and/or to prevent relapses.

Following therapeutic response:

a) in some patients, the treatment may be gradually withdrawn over a period of a few months and if relapse does not occur, administration will be stopped;

b) in other patients, a treatment may be undertaken for 12 months to prevent relapses, or continued longer, even for years with the objective to prevent recurrence of depressive episodes.

Accordingly, clinical trials with antidepressant medicinal products may be performed to assess therapeutic activity and safety during various types of acute depressive disorder. Nevertheless some specific studies – as already published – may also be conducted to substantiate the efficacy in preventing recurrences. This “prophylactic” effect of antidepressant medicinal products may be studied through phase III or IV trials.

12 Depression considered as a Syndrome

1.2.1 A medicinal product is to be considered an antidepressant only when it is shown to be effective in treatment of major depressive episodes. Major depressive episodes are depressive syndromes, which are distinguishable from the symptom alone by the severity and duration of the dysphoria and the presence of accompanying features e.g. psychomotor agitation or retardation, sleep disturbance, feelings of worthlessness or guilt, thoughts of death or suicidal attempts.

The consideration of the individual and family histories, the characterisation of the depressive syndrome and its quantification allow a classification (e.g. of primary/secondary, endogenous/non endogenous, and unipolar/bipolar depressions) but these distinctions may not be relevant to therapy.

For many existing medicinal products, it has not been possible to demonstrate initial therapeutic activity in patients v. placebo in less than 3-4 weeks exposure but the possibility in the future of new active substances with more rapid action cannot be excluded.

1.2.2 Antidepressant medicinal products are also used where the depressive syndrome is associated with other psychiatric manifestations or organic diseases. Specific studies should
be provided for each indication claimed in this field, even if the antidepressant activity has been correctly documented in several types of major depressive episodes.

The issue of mixed depression/anxiety requires adequate tools in order to evaluate separately the anxiolytic and antidepressant properties although anxiety may be integral to the syndrome of depression.

2. DIAGNOSTIC CRITERIA AND SELECTION OF PATIENTS

Patients entering a protocol should be defined according to internationally recognised criteria in order to build up homogeneous groups: either R.D (Research Diagnostic Criteria - Spitzer and Endicott), or D.S.M. III/R (Diagnostic and Statistical Manual of Mental Disorders) can be used. I.D. 10 (International Classification of Diseases - W.H.O.) can also be used if additional information on the actual type of depression is provided. Data files should be standardised according to one particular classification.

The selection of the patients includes not only a definition on the basis of diagnostic criteria but also a quantification of the severity of the depression. A sufficient severity of depression is necessary to demonstrate efficacy. While mild depression may not be distinguished by a placebo/active comparison, there is currently no evidence that medicinal products effective in moderate depression are also effective in severe depression. Adequate and unambiguous tools are needed. They should be used also, at regular intervals, for evaluating the response to treatment (see section 3).

The efficacy of a new antidepressant should be assessed in a chronological sequence (see section 8) on the following homogeneous sub-groups:
- different sub-groups of depressed patients should be assessed in order to establish the efficacy of the medicinal product and to determine double-blind fixed dose comparisons for different indications,
- patients with severe depressive syndromes,
- sub-groups of patients representative of the population in which the medicinal product could be useful. These studies should include sufficient numbers of elderly people or - in some cases - children. Subjects suffering from renal failure or liver insufficiency should not be forgotten.

3. ASSESSMENT OF EFFICACY

3.1 Basic criteria

The choice of tools used for the initial quantification (see section 2) and the subsequent evaluation of therapeutic changes must be specific, validated and reliable. Since no one technique of psychometric evaluation in itself is considered sufficient, varying combinations may be employed depending in part on the types of patients. These techniques involve observer and self rating scales. As observer scales are more sensitive and require fewer patients to test efficacy, these should be used in pivotal studies. Ideally the same tools should be used throughout the whole clinical evaluation of a medicinal product.

Immediate and repeated use of such tools should permit the evaluation of both the extent and rate of the therapeutic activity and its maintenance.
With regard to the prophylactic effect, the number of recurrences, their length and severity should be assessed over a lengthy period (see section 8).

3.2 Particular criteria

Actions of medicinal products on particular somatic or psychological symptoms associated with the depressive illness, such as anxiety, retardation, suicidal ideas, should also be determined.

4. USE OF PLACEBO

4.1 Comparison of the product versus placebo

4.1.1 Clinical studies should provide unambiguous evidence of the antidepressant activity and of the effective doses. It is well known that comparisons between a product and reference substances are difficult to interpret since there is a high placebo response rate in depression and the absence of a significant statistical difference does not necessarily indicate a therapeutic equivalence: such studies, to be meaningful, demand the recruitment of large numbers of patients.

Therefore, from a scientific point of view, randomised double-blind comparisons versus placebo, at an early stage of the development (see section 8), are preferable, to permit adequate evaluation of efficacy. Comparison to a placebo is also of value for distinguishing disease manifestations from adverse reactions of the medicinal product.

4.1.2 Ethically, the use of a placebo is however a controversial issue, specially when performing studies on the therapeutic activity on acute episodes.

Two general considerations favour placebo use:

- it would be detrimental to public health and ethically inadmissible, particularly in this field, to grant an authorisation to a medicinal product without providing unambiguous evidence of its activity,
- by reason of the large number of patients being included in comparative studies versus reference medicinal products (see section 4.1.1), the total number of therapeutic failures is or may be greater in such studies than in those comparing the product under test to placebo.

However, “concern for the interest of the subject must always prevail over the interest of science and society” (Declaration of Helsinki). Therefore, the comparison to placebo may only be contemplated provided precautions are taken to minimise the impact of the study (i.e. potential hazards of the study and the discomfort it may entail), such as:

- the inclusion of the smallest number of patients adequate to allow statistical evaluation,
- the exclusion of patients with serious suicidal risk,
- a short exposure time (not more than 4 weeks),
- a strict surveillance (with a continuous physical presence) in specialised units to prevent suicidal attempts,
- fail-safe provision whereby a serious deterioration of the patient's condition will allow withdrawal from the trial and standard therapy to be given under open conditions.
4.2 Run-in period
A run-in period, generally under placebo, single blind, is also often planned before starting the treatment period of therapeutic trials: this period is intended to ensure a wash-out, to carefully characterise and quantify patients, to verify that no rapid change of mood occurs in the absence of therapy or placebo. Placebo responders are ineligible for the study.

The duration of this run-in period is variable: a period of 3 to 7 days is generally regarded as relevant. However, in particular depending on the nature of previous treatment, it may be longer.

5. JUSTIFICATION OF THE DOSAGE REGIMEN
Although it is not possible to conduct such precise dose-ranging studies as those generally performed in other pathological situations, the doses used during the final phase of the clinical testing and thereafter proposed by the applicant, should be justified by controlled double-blind studies on two different dosage schedules determined from the preliminary non-controlled or open trials (see section 8). Plasma concentrations should be determined in specific studies.

For each dose level, individual steady-state plasma concentrations should be determined.

6. MONITORING OF ADVERSE DRUG REACTIONS
Adverse events should be carefully monitored at all stages of the investigation, preferably in relationship with plasma concentrations and routine laboratory tests.

6.1 It is important to differentiate the adverse reactions induced by the antidepressant medicinal product from overlapping disease symptoms (comparison with a placebo, scoring of possible undesirable effects prior to the onset of the trial).

6.2 Although the type of the predictable adverse reactions depend on the chemical nature and the mechanism of action of the antidepressant medicinal product (e.g. MAOI), attention is generally focused on blood dyscrasias; renal, hepatic, cardiac and neurological dysfunction and skin reactions; as well as on the possibility of sedation with modification of several activities and aptitudes, sleep disturbances, psychostimulant or anxiogenic effects, anticholinergic actions and cardiovascular actions.

6.3 All information related to overdosages should be available.

7. ASSOCIATED TREATMENTS
7.1 The possible influence of associated therapies (including psychotherapy and electroconvulsive therapy) on the outcome of clinical trials should be taken into account. Anxiolytic and/or hypnotic medicinal products often associated at the onset of an antidepressant treatment can bias the general assessment. For this reason, when such treatments cannot be avoided, the product and its dosage schedule should be defined before the trial; the equal distribution among the groups should also be analysed.
7.2 As a general principle, the interactions which can occur with the currently associated medicinal products (for example: another antidepressant medicinal product, anxiolytic or neuroleptic agents, lithium) or which seem possible in view of the class (for example: MAOI and anaesthetic or narcotic medicinal products), should be dealt with.

8. EFFICACY STRATEGY

8.1 Therapeutic activity

a) Initial trials intended to demonstrate the possibility of efficacy and the effective dose(s) are generally non comparative studies,

b) Next trials should consist of double-blind, (generally parallel) randomised comparisons of the test substance with a placebo (see IV) and/or established medicinal product(s) being used at therapeutic doses:
   - short-term studies are intended to fully demonstrate the antidepressant activity and determine the effective dose(s); unless otherwise justified, their duration should not be less than 4 weeks,
   - medium-term studies (3 to 6 months) are required to confirm the efficacy of the medicinal product as maintenance treatment.

In some of these studies, it is advisable to measure plasma concentrations to check the patients compliance, to look for a possible concentration-activity relationship and for inter-subject fluctuations.

If multicentre trials are performed, joint training sessions for observers should minimise variations in rating reporting.

8.2 Prophylactic action

In order to substantiate a prophylactic action, double-blind controlled studies with parallel groups should be performed. In manic depressive patients, the reference is lithium salts. In non-manic depressive patients, definitive comparisons of the test substance should be performed versus a placebo.

For a given patient, the duration of treatment depends on the rate of his/her recurrences; therefore it is necessary to know the length of the cycles in each individual subject.

As a general principle, the duration of such studies is at least one year, although 2 years or more may be necessary.

8.3 Safety

Acceptability and safety with full laboratory and clinical profile should be monitored for the duration of all trials. As for each medicinal product intended for long-term use, well documented clinical observations should be provided including at least 100 patients treated for 12 months (see note for guidance on Clinical Investigation of Medicinal Products for Long-Term Use).