NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF A MEETING HELD ON THURSDAY 8 MARCH 2000 AT 10.00 a.m. IN THE CONFERENCE ROOM ON THE 19th FLOOR AT MARKET TOWERS

Committee Members:

Present

Professor A M Breckenridge (Chairman)
Professor I V D Weller (Co-Vice Chairman)
Professor D Ashby
Professor T R E Barnes
Ms H Barnett
Professor A Blenkinsopp
Professor J Caldwell
Dr T L Chambers
Professor J K Chipman
Dr M J Donaghy
** Professor S J Eykyn
Dr J C Forfar
Professor H McGavock
Professor J M Midgley
Professor J F Smyth
Professor N C Thomson

[redacted]

Apologies

Dr M Armitage
Professor M J S Langman
Dr A P MacGowan
Professor J C Petrie

[redacted]

Professional Staff of MCA

Principal Assessors

[redacted]

Licensing Division

[redacted]

Post-Licensing Division

[redacted]

ES Division

[redacted]

Others

[redacted]

** Left after item 8
*** Left after item 7

1. **Announcements and Apologies**

1.1 The Chairman reminded the Committee that the papers and proceedings were confidential and should not be disclosed. Members were also reminded to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items.

1.2 Apologies had been received from Drs Armitage and MacGowan and Professors Langman and Petrie for the day.

1.3 [redacted]

1.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Papers

16. **CPMP Note For Guidance On Clinical Investigation Of Medicinal Products For The Treatment Of Bipolar Disorder**

The Committee noted the paper and endorsed the recommendations of Professor Barnes [redacted] as ***Annex D*** of the minutes.

[redacted]

18. **Any Other Business**

None.

19. **Date and time of Next Meeting**

The next meeting will take place **Thursday 23rd March 2000 at 10.00am**

ANNEX D

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTES FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF BIPOLAR DISORDER

INTRODUCTION (pages 1-2)

This revision of the CPMP guidelines seeks to redefine the main licensing indications for the treatment of bipolar disorder as *Treatment of acute manic episode* and *Prevention of manic/depressive episode* (section 1, page 2). It might be helpful to highlight this explicitly at the beginning of the document. These indications are discussed within the context of the Bipolar I and Bipolar II Disorder distinction. The guidelines suggest (section 3.3, page 4) that results from studies of Bipolar I Disorder "can probably be extrapolated to patients with Bipolar II disorder." Bipolar I Disorder is essentially acute mania, although the brief definitions of Bipolar I and Bipolar II Disorder (DSM IV) on page 1 of these guidelines disguise the fact that Bipolar I Disorder is actually a number of separate diagnoses (see Appendix 1), depending upon the nature of the affective episode most recently experienced (American Psychiatric Association 1994, National Institutes of Health 1995). We would be of the view that demonstration of therapeutic efficacy in Bipolar Disorder I cannot be extrapolated to efficacy for Bipolar II Disorder, which is principally depression. In other words, for any putative treatment of bipolar disorder it would seem appropriate for treatment efficacy to be separately established for the two categories. Few treatment trials have unequivocally demonstrated a positive effect for Bipolar II Disorder. Further, while treatment of Bipolar I Disorder does not run the risk of precipitating depression, with treatment of Bipolar II Disorder there is the potential complication of inducing rapid cycling.

DEFINITIONS (Section 2)

How the two treatment indications (*Treatment of acute manic episode* and *Prevention of manic/depressive episode*) might be operationally defined for the purposes of clinical trials seems to depend on the conceptual notions of treatment response in this area. One notion is that the treatment being tested is producing improvement related to a resolution of the pathophysiology underlying the acute episode. An alternative view, which is more commonly

held, is that the condition is essentially self limiting, with genuine resolution only being achieved naturally over time. Thus, medication produces only a symptomatic improvement, essentially masking the symptoms. On the basis of the latter hypothesis, relapse may occur despite a response to treatment: the illness being treated has not fully resolved and has 'broken through' the medication. However, the definition in the guidelines (page 3) refers to relapse only in terms of 'increase in symptomatology **immediately or almost immediately after medication is stopped**'.

There is a need for the definitions in the guidelines for relapse, recurrence, etc. to be rendered more specific and distinct, based on sound clinical concepts and experience of bipolar disorder. The use of a consistent terminology would enhance the overall clarity of the guidelines and provide a sound basis for determining optimal trial design and methodology. For unipolar depression, Frank et al (1991) produced helpful summary definitions for terms for 'designating change points' (response, remission, recovery, relapse and recurrence). It would also be useful to offer definitions for the continuation and maintenance phases of treatment. This might prevent confusion between the terms, as occurs in section 6.1. A concise summary of pragmatic definitions is offered in the figure in Appendix 2, which has been used by various authors (Kupfer 1991, Hirschfeld 1994, Lader 1994).

STUDY DESIGN

Acute manic episode (section 6.1, page 6)

Placebo-controlled studies of efficacy in acute mania are practicable up to 3 to 4 weeks, particularly as admission to hospital has an initial therapeutic effect. But over a longer period the drop-out rate in the placebo group is likely to be high, and render the findings difficult to interpret. To assess the maintenance of benefit, the guidelines recommend a placebo-controlled study comparing the new drug and a standard antimanic agent over twelve weeks. This would seem too long a period to sustain a viable placebo-controlled study. It would be necessary to allow withdrawal of patients from the study if there was clinical concern, so the dropout rate would almost certainly be very high. The use of a chlorpromazine- or haloperidol-sparing design ('rescue medication') is worth considering as a pragmatic strategy, but if the consequence were that the majority or all of the patients in the placebo group ended up receiving antipsychotic medication this could confound interpretation of the findings.

The third paragraph of section 6.1 describes a 12-week acute mania/continuation study. As currently written, the proposal is somewhat confusing. The recommended design seems to be a three-arm comparison of placebo, test product and active control for the first three weeks followed by a two-arm phase for the remaining nine weeks, comparing only test product and active control.

Recurrence prevention (sections 6.2 and 7.2.2.2)

Recurrence is the appearance of a new illness episode (see Appendix 2). The definition in the guidelines (section 2.1.4, page 3) refers to the 're-emergence of symptoms (new episode) after a time with no or minimal symptoms'. This definition does not specify whether or not this deterioration is in the context of continued medication or not. However, on the basis that that medication produces only a symptomatic improvement, recurrence could only be said to have occurred if full recovery in the absence of medication had already been demonstrated. Following this argument, the only way to establish prevention of recurrence in a clinical trial would be to withdraw medication from those showing a sustained remission with medication administered for a reasonable period (say, six months). Those maintaining their remission off treatment for a time would then be randomised to the drug treatment to be tested or an established treatment for a prolonged period, from 1 to 2 years.

One matter raised by such a methodology would be the interpretation of any deterioration following the drug withdrawal at six months. This could be relapse of the unresolved initial episode, a genuine recurrence of the disorder or possibly symptoms induced by medication withdrawal. For each patient, judgement on this might depend on the known periodicity of their illness and past evidence of deterioration related to drug withdrawal. The statements in the guidelines on the issue of prevention of manic/depressive episodes do not address these issues directly, and therefore there is no discussion as to whether or not such a methodology would be desirable or practicable.

In the context of clinical trials for depression, Hirschfeld (1994) suggests that randomisation (or re-randomisation) after acute stabilisation (12 weeks of treatment) would constitute a continuation study, while randomisation after completion of the continuation phase (after 6 months or more) would be a maintenance treatment study (see also Appendix 2). For bipolar illness, the guidelines similarly indicate that for studies of *recurrence prevention* (section 4.2, page 5) and *prevention of manic/depressive episode* (section 5.2, page 6) the distinction between

relapse and recurrence will need to be made pragmatically on the basis of duration of remission (see section 5.2). Explicit guidance is required for studies of bipolar disorder, along the lines provisionally proposed in Table 1. Section 6.2 refers to 'long-term trials' but gives no indication of duration, although 'at least one year' is offered in section 7.2.2.2. In line with the comments above, the use of placebo in such long-term prevention studies (see section 6.2) seems hard if not impossible to justify as viable, practical and ethically sound.

The guidelines suggest only patients with a 'reasonably high recurrence rate' are recruited into prevention studies (section 5.2, page 6). Presumably this reflects a concern that recurrence in bipolar patients is relatively infrequent (although more common than in patients with major depression) and therefore such studies would tend to have a lack of power.

For prophylactic studies of Bipolar Disorder I, there would be a need to need to regularly assess patients with the recommended mania and depression rating scales, perhaps every three months. Guidelines on the operational definition of recurrence would be useful. While many recurrences of mania would inevitably lead to readmission to hospital, inpatient stay might not be the best outcome measure. A broader, but clinically-relevant, definition of relapse would be symptom exacerbation requiring clinical intervention. A key relevant measure would be the use of additional medication. It might also be helpful if the guidelines provided advice on the potential value and relevance of assessing other clinical and social outcomes, such as functional disability and quality of life (Angst et al 1996).

SAFETY ASPECTS

The guidelines as currently drafted refer principally to side-effects of antipsychotics, lithium and mood stabilisers such as sodium valproate (although there is no mention of hyperammonaemia, which occurs at moderate levels fairly commonly with sodium valproate, and may very rarely lead on to encephalopathy, loss of seizure control and death).

REFERENCES

1. Angst J, Kupfer DJ, Rosenbaum JF. (1996) Recovery from depression: risk or reality? *Acta Psychiatrica Scandinavica* 93, 413-419.

2. Frank E, Prien RF, Jarrett RB, et al. (1991) Conceptualization and rationale for consensus definitions of terms of major depressive disorder: remission, recovery, relapse and recurrence. *Archives of General Psychiatry* 48, 851-855.

3. Hirschfield RMA. (1994) Guidelines for the long-term treatment of depression. *Journal of Clinical Psychiatry* 55 (suppl. 12), 61-69.

4. Kupfer DJ. Long-term treatment of depression. *Journal of Clinical Psychiatry* 1991; 52 (suppl.): 28-34.

5. Lader M. Current trends in the drug treatment of depression. *Hospital Update* 1994: 206-213.

TABLE 1

Provisional guidelines for short, medium and long-term treatment trials in bipolar disorder

Efficacy measure	Duration of trial	Evidence for efficacy
Short term: Treatment of acute manic episode.	3-4 weeks.	Improvement compared to pretreatment and placebo. Responder analysis. Equivalent to standard antimanic agent.
Medium term: Continuation treatment for prevention of relapse.	3-6 months.	Sustained improvement. Relapse rate equivalent to standard antimanic agent.
Long-term: Maintenance treatment for prevention of recurrence.	At least 1 year, preferably 2.	Sustained improvement. Benefit/risk ratio and recurrence rate for manic, hypomanic and depressive episodes equivalent to standard treatment agent.

APPENDIX 1

Bipolar I Disorder

- *Bipolar I Disorder, Single Manic Episode*
  Presence of only one Manic Episode and no past Major Depressive Episodes.
- *Bipolar I Disorder, Most Recent Episode Hypomanic*
  Currently (or most recently) in a Hypomanic Episode. There has previously been at least one Manic Episode or Mixed Episode.
- *Bipolar I Disorder, Most Recent Episode Manic*
  Currently (or most recently) in a Manic Episode. There has previously been at least one Major Depressive Episode, Manic Episode, or Mixed Episode.
- *Bipolar I Disorder, Most Recent Episode Mixed*
  Currently (or most recently) in a Mixed Episode. There has previously been at least one Major Depressive Episode, Manic Episode, or Mixed Episode.

Bipolar II Disorder

- Presence (or history) of one or more Major Depressive Episodes and at least one Hypomanic Episode. Additionally, there has never been a Manic Episode or a Mixed Episode.

References

6. American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders, Fourth edition*. Washington, DC: American Psychiatric Association.
7. National Institutes of Health, National Institute of Mental Health, NIH Publication No. 95-3679 (1995)

APPENDIX 2

Phases in a disorder and its treatment

From Kupfer DJ. *J Clin Psychiatry* 1991;52 (suppl.):28-34.