- D 715

INTERNATIONAL Pfizer SUBSIDIARIES

PFIZER U.K.I.

MEMORANDUM

Date: 26th April 1989

To: File Note - STL-UK-88-001B

From: E A Wickham

Subject: Meeting with Stuart Montgomery, Keith Lilley, Declan Doogan, Mike Aubry and E A Wickham, St Mary's Hospital, 24.4.89.

SERTRALINE

ACTION

We met to obtain Stuart Montgomery's advice on the sertraline studies and the use of his video on the MADRS scale for GP training purposes.

1. General discussion

Stuart Montgomery first gave us some background on the CSM decision on sertraline, which he said was borderline, initially going in our favour, but with concern then developing on the lack of information on hepatotoxicity in humans which should have been looked at following the animal findings. He suggested we should go for a hearing, and re-analyse the top dose data, especially with regard to hepatotoxicity. He thought we should also drop the reference to bipolar illness as an indication, as this inferred safety with lithium. Declan Doogan said a lithium interaction study had just been completed; Stuart Montgomery said we would need more than one, as the "serotonergic syndrome" (a neuroleptic malignant syndrome) is serious although rare - 4 deaths in 1 million patients in America.

Stuart Montgomery said that the long term prophylactic study had been regarded by the CSM as the major plank for efficacy - they were very impressed by it. At the recent launch of fluoxetine in France the prophylactic study had been considered to be very important by "opinion leaders" there. The CPMP will be asking for long term efficacy evidence in depression (and anxiety), and will discriminate between drugs which have proven short or long term efficacy - putting a restriction on the use of those without evidence of long term efficacy.

Stuart Montgomery considers that every episode of depression should be treated for a minimum of 4 months. The WHO are recommending 6 months. The Mindham (MRC) prophylactic study showed an equal incidence of recurrence in their patients with first episodes and those with previous episodes. 60% of patients who present with what is apparently a first episode will turn out to be recurrent depressives.

ACTION

The reduction in benzodiazepine prescribing has led (unexpectedly) to a reduction in antidepressant prescribing. GPs are "appalling" at diagnosing and treatment of depression - there is a major task to be done in educating them.

PFIZERS!?

The CSM had objected to fluoxetine because it was perceived as increasing nervousness and agitation, and could therefore be associated with increased suicide. Lilly did an analysis of all their data and showed that patients with agitated depression did better on fluoxetine than on tricyclics - we should do a similar analysis, taking all the patients with a Hamilton agitation score of 2, 3 or 4 from our data base and comparing the effect of sertraline, comparators and placebo.

DD?

Stuart Montgomery is convinced that anxiety and aggression are linked with serotonin (zimelidine was found to have an anxiolytic effect) and this has "tremendous marketing implications". Sedation (with tricyclics) does not go with an anxiolytic effect.

Evidence is needed to show that tricyclics do not work in obsessive compulsive disorder (OCD), whereas serotonin re-uptake inhibitors (SRIs) do. CPMP guidelines will be produced on OCD, panic disorders (where all patients with concomitant depression will have to be excluded), dysthymia and recurrent brief depression ("atypical" depression affecting 5% of the general population with 12 or more episodes per year of 3-4 days' duration, socially crippling, associated with aggressivity and suicide and mislabelled as dysthymia - very much a European illness). Draft guidelines are already out on minimal cognitive defects.

Stuart Montgomery considers that anxiety will become "absorbed into depression" and it will become necessary to show anti-anxiety efficacy as well as antidepressant. We should be looking at anxiety states. Is panic disorder a symptom of depression. We should be looking at panic disorders - fluvoxamine and fluoxetine will come out with evidence in these.

American data on OCD will tend to be rejected in Europe because American rating scales are prejudiced towards severe pathology. We should do a study in Europe, going for a crossover design (as for chlomipramine studies).

CONFIDENTIAL

ACTION

2. Sertraline studies

We then discussed the acute protocols against dothiepin. Stuart Montgomery considered that Boots' dosage restriction was very clever and that we should be wary of providing them with efficacy data against placebo which they did not have. He did not like the idea of GPs having to look at side effects to determine dose increase, as he considered they would have difficulty distinguishing between side effects and depressive symptoms. If we were going to have to increase dothiepin dosage from 75mg to 100mg, we should do so at 1 week rather than at 2 weeks, which would result in a high drop-out rate on dothiepin due to side effects. By 2 weeks, patients have learnt to live with side effects. He thought we should put up the sertraline dose from 50mg to 100mg on the same criteria as for dothiepin, ie lack of side effects at the lower dose, regardless of efficacy. Alternatively, we could reduce the study duration to 4 weeks and keep the sertraline dose at 50mg. Any non-responders could then be put on 100mg sertraline openly for 2 weeks.

Another possibility would be to omit the dothiepin group from the placebo-controlled study, on the basis that the main objectives of these studies are (a) to show efficacy of sertraline in general practice, and (b) to show a better side effect profile of sertraline against dothiepin. This could be achieved without including dothiepin in the placebo-controlled study. We could then put more patients into the sertraline and placebo groups in this study to reduce the risk of a negative result.

Regarding the long-term study, Stuart Montgomery thought we could include all responders from the acute studies, whether or not they had a previous episode, as long as we minimised for this factor. Patients who had not been in the acute studies could be included, as long as they had not been treated for more than 8 weeks with an antidepressant. The CGI score should not be used as an inclusion criterion - only an MADRS of under 15. Patients should be withdrawn if the MADRS rose to over 22 and this persisted when they were seen a week later.

The acute studies are now at an advanced stage of planning and approvals. A change of direction now will delay the start from 1st June to 1st September. Stuart Montgomery's concerns may be valid, but I still consider that our original plan for two acute studies against dothiepin, one with and one without a placebo group, is a sound approach to achieving our objectives. If we believe that sertraline in general practice will prove to be superior to dothiepin in terms of efficacy and side effect profile, then we have to be prepared to put this to the test.

ACTION

The long-term study remains an important part of the overall plan. I need to revise the protocol and get it to Keith Lilley for re-costing on the basis of smaller sample sizes.

EAW

pp E A Wickham

EAW/aw

cc: Dr E A Stevens
Mr M L Aubry
Dr D Doogan

Meeting with Dr.S.Montgomery,

at St.Mary's Hospital, London

on Monday 24th April 1989

SERTRALINE

Dr.Montgomery gave some background on the CSM response to the Sertraline product licence application. He said that Sertraline was almost approved without a Section 21 letter. The efficacy package was accepted essentially without comment. The safety analyses require re-presentation. This related principally to liver function. He said that the general view was that the drug was probably not hepatotoxic but the way the data was presented did not allow the conclusion to be reached. The pre-clinical issues were not discussed.

He commented that the medical reviewer was pleased with the prompt and helpful responses from the company when additional data requests were made. This contrasted with that of Lilly when fluoxetine was being reviewed.

The fluoxetine PLA was held up for a considerable period because of lack of long term data, the concern that the compound was stimulant and side-effects.

Dr.Montgomery advised us to analyse individual HAM-D items and look at the anxiety/agitation items by a meta analysis if necessary. Fluoxetine significantly improved these items compared with active comparative agents and placebo. Fluvoxamine has shown similar anxiolytic activity. This helps to answer the side-effect questions relating to stimulation. He believes strongly that these 5HT uptake inhibitors and serotonergic drugs can show evidence of non-sedative anxiolytic activity.

We should exclude bipolar patients from the indications sections as this implies the compound can be given safely with lithium. It is now known that concurrent administration of serotonergic compounds with lithium may produce the potentially lethal serotonergic syndrome.

Our long term study was the "plank" on which the efficacy chaim could be supported. The new CPMP guidelines demand long term efficacy data. As yet Sertraline would still be the first compound to have the long term claim.

He advised us that we must appeal against the Section 21 letter and he would still like to remain a disinterested party at the CSM till the appeal was heard. Thereafter he would be happy to act as an adviser to Pfizer and declare an interest.

D.P.Doogan

DPD/CB/FQ0/27.4.89

c.c Dr.J.A.Milson
Dr.J.T.Henderson
Dr.D.McGibney
Dr.E.A.Stevens
Dr.J.I.Shaw

CONFIDENTIAL

058 000135

Motus/Pfizer

- D 715

INTERNATIONAL Pfizer SUBSIDIARIES

PFIZER U.K.I.

MEMORANDUM

SERTRALINE

Date: 26th April 1989

To: File Note - STL-UK-88-001B

From: E A Wickham

Subject: Meeting with Stuart Montgomery, Keith Lilley, Declan Doogan, Mike Aubry and E A Wickham, St Mary's Hospital, 24.4.89.

ACTION

We met to obtain Stuart Montgomery's advice on the sertraline studies and the use of his video on the MADRS scale for GP training purposes.

1. General discussion

Stuart Montgomery first gave us some background on the CSM decision on sertraline, which he said was borderline, initially going in our favour, but with concern then developing on the lack of information on hepatotoxicity in humans which should have been looked at following the animal findings. He suggested we should go for a hearing, and re-analyse the top dose data, especially with regard to hepatotoxicity. He thought we should also drop the reference to bipolar illness as an indication, as this inferred safety with lithium. Declan Doogan said a lithium interaction study had just been completed; Stuart Montgomery said we would need more than one, as the "serotonergic syndrome" (a neuroleptic malignant syndrome) is serious although rare - 4 deaths in 1 million patients in America.

Stuart Montgomery said that the long term prophylactic study had been regarded by the CSM as the major plank for efficacy - they were very impressed by it. At the recent launch of fluoxetine in France the prophylactic study had been considered to be very important by "opinion leaders" there. The CPMP will be asking for long term efficacy evidence in depression (and anxiety), and will discriminate between drugs which have proven short or long term efficacy - putting a restriction on the use of those without evidence of long term efficacy.

Stuart Montgomery considers that every episode of depression should be treated for a minimum of 4 months. The WHO are recommending 6 months. The Mindham (MRC) prophylactic study showed an equal incidence of recurrence in their patients with first episodes and those with previous episodes. 60% of patients who present with what is apparently a first episode will turn out to be recurrent depressives.

Meeting with Dr.S.Montgomery,

at St.Mary's Hospital, London

on Monday 24th April 1989

SERTRALINE

Dr.Montgomery gave some background on the CSM response to the Sertraline product licence application. He said that Sertraline was almost approved without a Section 21 letter. The efficacy package was accepted essentially without comment. The safety analyses require re-presentation. This related principally to liver function. He said that the general view was that the drug was probably not hepatotoxic but the way the data was presented did not allow the conclusion to be reached. The pre-clinical issues were not discussed.

He commented that the medical reviewer was pleased with the prompt and helpful responses from the company when additional data requests were made. This contrasted with that of Lilly when fluoxetine was being reviewed.

The fluoxetine PLA was held up for a considerable period because of lack of long term data, the concern that the compound was stimulant and side-effects.

Dr.Montgomery advised us to analyse individual HAM-D items and look at the anxiety/agitation items by a meta analysis if necessary. Fluoxetine significantly improved these items compared with active comparative agents and placebo. Fluvoxamine has shown similar anxiolytic activity. This helps to answer the side-effect questions relating to stimulation. He believes strongly that these 5HT uptake inhibitors and serotonergic drugs can show evidence of non-sedative anxiolytic activity.

We should exclude bipolar patients from the indications sections as this implies the compound can be given safely with lithium. It is now known that concurrent administration of serotonergic compounds with lithium may produce the potentially lethal serotonergic syndrome.