Bad Homburg,
May 25, 1984
BvK/AM

Eff Index Ratio: Therapeutic effect / Side effect

Mr. J. Harper, London
Dr. J. Kuzmierek, Erl Wood
Mr. S. A. Taural, London
Mr. D. Thompson, Indianapolis
Dr. L. Thompson, Indianapolis

F L U O X E T I N E

Yesterday we unofficially received a copy of the medical comment on our Fluoxetine application. A translation is attached.

Kind regards,

B. v. Kleist

B. v. Keitz, Bad Homburg

[redacted]

Pz 281 1522

ICL

Comment on the clinical documentation

As the preparation in hand is intended for the consumer in the Federal Republic of Germany, the indications, which were worked out according to the criteria effective in the United States, have to be adaptad to the German criteria and to be worded understandable.

The indications suggested by the manufacturer "depressive disorder" are worded unprecise and partially misleading. Already with consideration of the american criteria for assessment of the efficacy of the preparation, it can be said, that the preparation has not shown the same efficacy in all depressive disorders.

In the Federal Republic of Germany the nosological classification of depressions, which is in accordance with the WHO classification, has established itsself and proved usefull. From this classification the basic therapy, the progress, the prognosis and the indication for a prophylactic longterm therapy can be directly derived. That the preparation may not be equally effective in all types of depression, can be predicted from its mode of action; antidepressants, who complement deficiencies of transmitters resp. compensate an unbalance of transmitters are only effective in endogenous and partially also in psychogenic depressions.
or retarded

For a promissing therapy of depression besides the nosological also the phenomenological aspects have to be considered. Considering the criteria used by the american investigators these aspects can not be directly transferred to the German conditions.

yes?

Further condition for a promissing therapy is the choice of an antidepressant with a profile of action, which is right for the clinical picture. On grounds, of the submitted studies the profile of action of the preparation is hardly identifiable: perhaps it posseses a slight anxiolytic activity. But this would have to be proved convincingly by additional clinical studies.

In the studies up to 17 criteria for exclusion were stated.

Of the 46 attached study protocols in 25 the note is to be found, that these studies are not completed. Each double-blind study is praceded by a one week placebo wash out period. As statements on the medications, which were used in the pretreatment of the depression, are missing, the question occurs, if firstly this period was not to short and on the other hand, if a carry-over-

PN 281 1523

first examination before the beginning of the studies.

The comparison studies with standard antidepressants and with placebo gave most variable results. In 3 studies the preparation showed no efficacy, in others it was equally effective. Only in the imipramin study the preparation showed itsself to be more effective in individual of the studied parameters.

Nearly all authors of the double-blind studies point out, that the number of patients was to small to detect differences in the efficacy between the comparison drug and the study medication.

Most self-rating methods, which are decisive for the assessment of the efficacy of the preparation indicate little resp. no improvement in the clinical picture of the patients during treatment with the preparation at hand.

Most studies were conducted under ambulatory conditions. Hence it follows, that the investigators had not the possibility to observe the clinical picture continuously, which in depressive patients varies greatly during the day. Even on ground of this fact it can be said, that the submitted studies indicate an improvement of the studied parameters, but not of the illness itsself.

The use of the same criteria for the assessment of the efficacy of the preparation independent from the age of the patient is from a clinical standpoint inadmissible. For depressions in advanced age the cerebro-organic factor plays a very important role. No psychometric method was applied to eliminate this factor.

From the 1427 patients treated with the preparation a group of 38 patients was formed, in whom EEG examinations were done. These examinations, which proved an aggravation of the findings (rhythm retardation, abnormal synchronisation) at continual therapy, should have been done in small groups of patients in each stage of the clinical trials with varing doses of the preparation.

No neuro-endocrinological examinations were done, which are necessary during the clinical trial of a new antidepressant.

The frequency of side-effects was very high (partly more than 90%) and the side-effects resulted nearly in each study in drop-outs. The frequency of side-effects depended on the dose, the age and the duration of therapy. Deceiding for the clinical significance of side-effects is not only the frequency of their occurance but also their severity.

The authors of most studies pointed out, that the preparation on ground of its pharmacokinetic properties (low clearance, long half-lives) accumulates even when given once daily.

In the clinical trials pathological ophtalmonological and pulmonary conditions are found almost regularly. It should be considered, if these are not illnesses, which were observed in animals in an other appearance in the same organs. During the clinical trials unfortunately no further examinations were done to clarify these aspects of side-effects. As long as there is not sufficient experience with the preparation, eye and lung examinations have to be arranged at regular intervals.

During the treatment with the preparation the laboratory chemical and enzymatic examinations showed deviations from the normal range, which partly indicate severe damage of the corresponding organ resp. system. The expert has already pointed out these deviations in his opinion and commented on them accordingly, so that they need not be repeated here.

In 15 - 20% of cases side-effects occur, which involve the central nervous system. As most of them resemble the clinical picture of the underlying disease, even from theoretical reasons one has to expect an intensification and not an improvement of symptoms.

During the treatment with the preparation 16 suizide attempts were made, 2 of these with success. As patients with a risk of suizide were excluded from the studies, it is probable that this high proportion can be attributed to an action of the preparation in the sence of an deterioration of the clinical condition, which reached its lowest point.

No studies were done, from which the tolerance of a combination therapy with other antidepressants as well as neuroleptics can be concluded.

The results of the conducted studies do not allow any conclusions on, whether with long-term therapy with the preparation the developement of dependance and tolerance is to be expected.

Summarizing opinion

1. The claimed indication "depressive disorders" can not be accepted in this form. The entire studies have to be reworked with consideration of the criteria of the science of depression effective in the Federal Republic of Germany as well as with reference to the WHO criteria, so that they are understandable for the physician and the patiant.

2. Considering the benefit and the risk, we think this preparation totally unsuitable for the treatment of depression.

25. Mai 1984
BvK/AM