OAA 0121 14:40GMT
IN04 0068 15:55GMT 06/26/84

ZCZC OAA121 GE1006
GL IND1
.GE1EL 06261440

ASHBROOK, EM (IND1) *IND1* 31/2
HARDISON, CD (IND1) *IND1* 22/3
STARK, P (IND1) *IND1* 31/2 ***
CC.: ARGAY, DA (IND1)
BANDAK, S (HQPA)
GODWIN, S (HQPA)
HEYMANNS, S (GE1)
VON KEITZ, B (GE1)
KOESTENBERGER, S (GE1)
KUSMIEREK, J (ERL)
SPICKSCHEN, T (GE1)
STEINMEYER, HG (GE1)
THOMPSON, WL (IND1) *IND1* 31/2
WAEGER, A (GE1)
WEINSTEIN, AJ (IND1) *IND1* 31/2
WOLD, J (ERL)
ZERBE, RL (IND1) *IND1* 31/2
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BAD HOMBURG JUNE 26, 1984 GLA
TELEX NO. 005

RE.: FLUOXETINE - REGISTRATION GERMANY

THIS IS TO CONFIRM, WHICH ADDITIONAL DATA HAVE BEEN IDENTIFIED TO BE ESSENTIAL DURING OUR DISCUSSION AT THE BGA (JUNE 15, 84). ALL THE ISSUES WERE SUBJECT TO VARIOUS DISCUSSIONS WITH MEDICAL MARKETING PERSONS ON THE OCCASION OF THE FLUOXETINE SYMPOSIUM / 14 TH C.I.N.P. CONGRESS:

1. EFFICACY DATA ON PATIENTS OF NON-ENDOGENOUS SUBTYPE. THIS COULD HELP US TO ACHIEVE THE ''REACTIVE DEPRESSION'' CLAIM.

2. THE BGA STATED THAT THERE IS A DISAGREEMENT BETWEEN PATIENT'S AND DOCTOR'S JUDGEMENT OF EFFICACY. SINCE IN THEIR OPINION THE PATIENT'S IMPRESSION IS MORE IMPORTANT, WE HAVE TO DEMONSTRATE CORRELATION BETWEEN SCL 58 AND HAMD AND CGI AND PGI RESP. (PERHAPS BY GRAPHS ?).

3.A A CRITICAL ISSUE FOR THE BGA IS SAFETY IN LONG-TERM TREATMENT. PATIENT NUMBERS OF 218 AND 74 TREATED FOR MORE THAN ONE HALF AND ONE YEAR RESP. MAY POSSIBLY NOT SATISFY OUR AUTHORITIES. THEIR CONCERNS ARE LEUKOPENIA / AGRANULOCYTOSIS, HEPATOTOXICITY

AND POSSIBLE DAMAGE DUE TO PHOSPHOLIPIDOSIS (CONCERNING THE LATTER SEE 15).
SINCE THE DATA BASE HAS BEEN ENLARGED DURING THE PAST YEAR THE QUESTION IS, WHETHER YOU COULD PROVIDE US WITH THE RESP. SAFETY DATA ON INCREASED PATIENT NUMBERS.

B EVALUATION OF RECURRENCIES DURING LONG-TERM TREATMENT.

4. IN THE CONTROLLED TRIALS WE HAD ALL THE CONTRAINDICATIONS OF TRICYCLIC COMPARATORS (E.G. GLAUCOMA, URINARY RETENTION, SEVERE CARDIOVASCULAR DISEASE, ETC.) AS EXCLUSION CRITERIA. WE HAVE TO DEMONSTRATE - PERHAPS BY ANALYSIS OF OPEN TRIALS - THAT FLUOXETINE IS SAFE IN SUCH PATIENTS. OTHERWISE WE WILL HAVE TO NAME THOSE EXCLUSION CRITERIA ALSO AS CONTRAINDICATIONS IN THE PACKAGE INSERT.
THE SAME APPLIES TO SERIOUS SUICIDAL RISK, BIPOLAR ILLNESS, HYPERTENSIVE PATIENTS TREATED WITH CERTAIN ANTIHYPERTENSIVE DRUGS, HISTORY OF SEIZURES, HYPERTHYROIDISM.

5. POOLED IN-PATIENT DATA

6. ANALYSIS OF PRETREATMENT WITH OTHER ANTIDEPRESSANTS, NEUROLEPTIC DRUGS, OR TRANQUILIZERS (TO DEMONSTRATE THAT ONE WEEK OF WASH-OUT WAS SUFFICIENTLY LONG).

7. THE BGA EXPLAINED THEIR RESERVATIONS REGARDING CNS SIDE-EFFECTS:

THERE HAVE BEEN A FEW PATIENTS COMPLAINING OF PSYCHOSIS AND HALLUZINATIONS.
PLEASE PROVIDE US WITH DETAILED REPORT, WHETHER THOSE PATIENTS SUFFERED FROM ''PSYCHOTIC DEPRESSION'', WHETHER THE HALLUZINATIONS DEVELOPED DURING TREATMENT OR HAVE PERHAPS BEEN PRESENT ALREADY AT START OF TREATMENT, OR WHETHER THOSE EVENTS MAY INDEED BE INTERPRETED BY ''AGGRAVATION OF DISEASE''.

8. PLEASE CONFIRM THAT A TOLERANCE TO FLUOXETINE DID NOT DEVELOP (DOSE OVER TIME) AND WITHDRAWAL SYMPTOMS HAVE NOT BEEN OBSERVED AFTER LONG-TERM TREATMENT (LONG ELIMINATION HALF-LIFE)

9. ALL KINDS OF SAFETY DATA WE HAVE ON CONCOMITANT INTAKE OF NEUROLEPTIC OR OTHER ANTIDEPRESSANT DRUGS.

10. COMPARATIVE USE OF CONCOMITANTLY TAKEN HYPNOTICS AND BENZODIAZEPINES IN AGITATED / RETARDED FLUOXETINE PATIENTS VERSUS AGITATED / RETARDED PATIENTS ON COMPARATORS.
REASON: THE BGA SUSPECTS FLUOXETINE TO BE A STIMULATING / ACTIVATING DRUG (SIDE-EFFECT PROFILE, SUICIDES, SUICIDE ATTEMPTS).

11. WE HAVE TO EVALUATE THE APPROXIMATE TREATMENT DURATION UNTIL ANTIDEPRESSANT EFFICACY USUALLY BECOMES EVIDENT (FOR PACKAGE INSERT INFORMATION).

12. THE BGA STATED THAT DUE TO THE ACCUMULATION OF FLUOXETINE WE SHOULD CONSIDER TO RECOMMEND A LOWER MAINTENANCE DOSE AFTER HAVING ACHIEVED A CERTAIN RELIEF OF ACUTE SYMPTOMS.
THEY ADVISED TO GIVE CLEAR INSTRUCTIONS CONCERNING DOSE-

ADJUSTMENT WITH TIME.

13. WE SHOULD CLEARLY DEFINE THE MAXIMUM DURATION OF TREATMENT WHICH WE ARE GOING TO RECOMMEND.

14. AS WE ALREADY EXPLAINED BY OUR TELEX TO DR. ZERBE OF JUNE 8, '84 WE NEED A CAREFUL ANALYSIS OF SUICIDES AND SUICIDE ATTEMPTS: PATIENT BY PATIENT, SYMPTOMATOLOGY / SEVERITY UPON ENTRY INTO THE STUDY AND WEEK BY WEEK UNTIL THE EVENT OCCURRED, DOSE OF FLUOXETINE, SIDE-EFFECTS, ETC.
THIS IS A VERY SERIOUS ISSUE IN THE OPINION OF THE BGA.
IT MIGHT WELL BE THAT WE WILL HAVE TO RECOMMEND CONCOMITANT TRANQUILIZER INTAKE FOR THE FIRST 2 OR 3 WEEKS IN THE PACKAGE LITERATURE.

15. THE MOST IMPORTANT ISSUE IS THE LUNG AND EYE FINDINGS DURING FLUOXETINE TREATMENT.
THE BGA STATED THAT WE DID NOT APPLY NEWER TECHNIQUES (E.G. SCANNING, TOMOGRAPHY, BIOPSY) TO SUBSTANTIATE, WHETHER THE CHANGES FROM NORMAL TO ABNORMAL WERE DRUG RELATED OR NOT. THE BGA CANNOT RULE OUT A DAMAGE SIMILAR TO THAT SEEN IN ANIMALS DUE TO PHOSPHOLIPIDOSIS.

ACTIONS, WHICH COULD HELP IN A NOT VERY PROMISING SITUATION:

A) OBTAIN OPINIONS FROM OPHTHALMOLOGIST AND PULMONOLOGIST, WHO HAVE EXAMINED FLUOXETINE PATIENTS
B) PROVIDE DETAILED REPORT ON LYMPHOCYTE INVESTIGATIONS.
C) INVOLVE PROFESSOR LUELLMANN

PLEASE EXCUSE IF THERE ARE SOME OF THE ISSUES ALREADY COVERED BY THE DATA WE RECEIVED IN THE MEANTIME.
WE HAD NOT ENOUGH TIME TO GO THROUGH IN DETAIL.
WE APPRECIATE ALL THE HELP WHICH WAS SPONTANEOUSLY OFFERED BY THE INDIANAPOLIS AND LONDON / ERL WOOD GROUPS OF STATISTICIANS, MEDICAL AND MARKETING COLLEAGUES.
NEVERTHELESS IT WILL BE A DIFFICULT EXERCISE FOR A FINAL SUCCESSFUL OUTCOME.

REGARDS
SCHENK, J (GE1)
WEBER, HJ (GE1)

#06261443
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