CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-031/S-026

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

ITEM 13/14 - PATENT INFORMATION

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

Patent No.	Expiry Date	Type of Patent	Patent owner
4 721 723	December 29, 2006	Drug	Beecham Group p.l.c. Brentford, England
5 872 132	May 19, 2015	Drug	SmithKline Beecham Corp.
5 900 423	May 19, 2015	Drug	SmithKline Beecham Corp.

EXCLUSIVITY SUMMARY for NDA # 20-031 SUPPL # S-026
Trade Name Paxil Generic Name paroxetine HCl

Applicant Name GlaxoSmithKline HFD- 120

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-031 _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Study 641

Investigation #2, Study # Study 642

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # Study 641

Investigation #__, Study # Study 642

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 23,280 YES /_X_/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # 23,280 YES /_X_/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

/S/ 4/13/01

Signature of Office of Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD-120/Homonnay
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Paxil tablets (paroxetine) for the treatment of generalized anxiety disorder

TO: File NDA 20-031/S-026
[**Note:** This overview should be filed with the 4-28-00
original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, panic disorder, and social anxiety disorder in an immediate release tablet, i.e., Paxil (NDA 20-031, originally approved for depression in December, 1992). S-026 provides data in support of a new claim for this same Paxil tablet in the treatment of generalized anxiety disorder (GAD) in a dose range of 20-50 mg/day.

It should be noted that, at the current time, there are a number of older drugs, mostly benzodiazepines, approved for the treatment of what is now known as GAD. At the time of these approvals, the approach to labeling was to grant a claim for the "management of anxiety disorders or for the short-term relief of the symptoms of anxiety." Buspirone (Buspar), a nonbenzodiazepine compound with a primary serotonergic effect, i.e., it's a prominent 5HTA1 agonist, is a more recent drug that was approved for a similar claim in 1985. More recently, venlafaxine (Effexor XR), a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of neuronal dopamine reuptake, was the first drug approved explicitly for GAD (3-11-99).

Given the symptom overlap in patients with depression and GAD, one of the concerns identified early in the development of this new indication for venlafaxine was how this overlap would be sorted out in making a judgement regarding the specific benefit of this product in GAD. During the review of the Effexor XR

application for GAD, we were persuaded that there was an effect of this drug specific to GAD that would justify this specific claim.

We held an end-of-phase 2 meeting with SKB on 9-3-98 to discuss the sponsor's development program for Paxil in GAD. We generally endorsed the planned program, but did indicate that we would need to address the question of specificity of response to GAD, e.g., by showing an effect on HAM-A items 1 (anxiety) and 2 (tension).

Since the proposal is to use the currently approved Paxil immediate release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutical reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Karen Brugge, M.D., from the clinical group. Kallappa Koti, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND 23,280. The original supplement for this expanded indication (S-026) was submitted 4-28-00.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Paxil tablets are already marketed, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Paxil tablets are already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Paxil tablets are already marketed, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 3 double-blind, randomized, 8-week, placebo-controlled trials (641, 642, and 637) in adult outpatients meeting DSM-IV criteria for generalized anxiety disorder (GAD). The identified primary outcome measure for these studies was change from baseline for the Hamilton Anxiety Rating Scale (HAM-A) total score. The HAM-A is a widely used instrument in evaluating treatments for GAD, and has been shown to be sensitive to drug effects. Its total score ranges from 0 to 56 (14 items with ratings from 0-4). There were several secondary outcome measures in these trials, including, among others, HAM-A items 1 (anxiety) and 2 (tension), and the CGI.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 641

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (50 US and Canadian sites) comparing paroxetine immediate release tablets (20 or 40 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for GAD. Patients were started at 10 mg, and doses were increased at 10 mg weekly increments until the assigned dose was reached. Patients could not have other Axis I disorders, in particular, major depression. However, patients with co-morbid dysthymic disorder could be included. There were 180-197 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 73-78%.

Overall, the HAM-A total score results from this study consistently favored paroxetine over placebo for both dose groups at weeks 6 and 8 for both LOCF and OC analyses. The p-values were < 0.001 at week 8 for both doses in the OC analyses, and < 0.001 and < 0.01, respectively, for the 20 and 40 mg/day doses in the LOCF analyses. Dunnett's test was used to adjust for the two doses. For the CGI Improvement, 80% of paroxetine 40 mg completers and 68% of paroxetine 20 mg completers met the response criterion (score of 1 or 2) compared to 52% for placebo. For the HAM-A total score, the difference between paroxetine and placebo in mean change from baseline for both the LOCF and OC analyses at 8 weeks, for both 20 and 40 mg, was roughly 3 units. Paroxetine was also superior to placebo for both dose groups, both LOCF and OC analyses, for HAM-A items 1 and 2.

5.1.2.2 Study 642

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (35 US and Canadian sites) comparing paroxetine immediate release tablets (20 to 50 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for GAD. Patients were started at 10 mg and were titrated in weekly increments of 10 mg. Patients could not have other Axis I disorders, in particular, major depression. However, patients with co-morbid dysthymic disorder could be included. There were roughly 150 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 77-81%. The mean week 8 paroxetine dose for completers was 37 mg.

Overall, the HAM-A total score results from this study consistently favored paroxetine over placebo at weeks 6 and 8 for both LOCF and OC analyses. The p-values were 0.006 at week 8 in the OC analysis, and 0.008 at week 8 in the LOCF analysis. For the CGI Improvement, 72% of paroxetine completers met the response criterion (score of 1 or 2) compared to 56% for placebo. For the HAM-A total score, the difference between paroxetine and placebo in mean change from baseline for both the LOCF and OC analyses at 8 weeks was roughly 2.5 units. Paroxetine was also superior to placebo, on both LOCF and OC analyses, for HAM-A items 1 and 2.

5.1.2.2 Study 637

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (50 European sites) comparing paroxetine immediate release tablets (20 to 50 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for GAD. Patients were started at 20 mg and were titrated in weekly increments of 10 mg. Patients could not have other Axis I disorders, in particular, major depression. However, patients with co-morbid dysthymic disorder could be included. There were roughly 185 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 82-88%. The mean week 8 paroxetine dose for completers was 27 mg.
Overall, the HAM-A total score results from this study did not favor paroxetine over placebo at weeks 6 or 8 for the LOCF analysis. The p-values were 0.111 at week 6 and 0.171 at week 8, in the LOCF analyses. Paroxetine was superior to placebo in the OC analysis, for both week 6 (p=0.001) and week 8 (p=0.005). For the CGI Improvement, 73% of paroxetine completers met the response criterion (score of 1 or 2) compared to 55% for placebo. For the HAM-A total score, the difference between paroxetine and placebo in mean change from baseline at 8 weeks was 1.1 units for the LOCF and 2.3 for the OC analyses. Paroxetine was superior to placebo, on both LOCF and OC analyses, for HAM-A item 1, and on the OC analysis for item 2.

5.1.3 Comment on Other Important Clinical Issues Regarding Paxil for Social Phobia

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 3 studies in the development program, two involved flexible dosing in a range of 20-50 mg/day (642 & 637), and thus, provided no evidence pertinent to the issue of dose response. The mean doses for completers to 8 weeks in these two studies were 37 and 27 mg/day, respectively, but these findings are not interpretable regarding dose response since patients in such trials are often pushed to the higher end of the permitted dose range, regardless of need. Study 641 was most informative regarding dose response, and this study suggested no advantage at a dose of 40 mg compared to 20 mg/day. Thus labeling must be clear in noting that the only pertinent evidence suggests no benefit in doses above 20 mg/day.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender. There was no indication of differences in response based on gender.

Size of Treatment Effect

It is difficult to clinically interpret the effect sizes on the measures observed for these 3 studies in terms of differences between drug and placebo in change from baseline. HAM-A total scores were roughly 24 for the 2 positive studies at baseline, and in the LOCF analyses, there were decreases of roughly 12 units at the week 8 endpoint for patients assigned to paroxetine. As is the case for other psychiatric indications, the mean score after treatment was still within a range that would be considered clinically ill. On the other hand, these changes are consistent with those seen for other drugs believed to be effective for GAD, so I am inclined to consider this a clinically relevant treatment effect.

Duration of Treatment

There were no data presented in this supplement pertinent to the question of the long-term efficacy of Paxil for GAD.

Specificity of Response for GAD

Although there was a finding of greater improvement on the MADRS in patients on paroxetine compared to placbeo, this is not surprising, given the overlap in symptoms of various depressive disorders and GAD. Patients with significant depression were not enrolled in these trials. In addition, these studies showed superiority of paroxetine over placebo on items 1 (anxiety) and 2 (tension) of the HAM-A, both considered reasonably specific for GAD. Thus, I consider this a reasonable demonstration of a specific response to paroxetine in patients with GAD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of a beneficial effect of Paxil tablets in the treatment of GAD. Studies 641 and 642 are both positive, both on the primary outcome and most secondary outcomes, and study 637 shows effect sizes of the same magnitude and is at least supportive. The sponsor is currently conducting a relapse prevention trial. Since GAD is also a disorder found in the pediatric population and, once approved for this indication, Paxil will likely be used in pediatric patients, we will require adequate and well-controlled trials of Paxil for GAD in this population as well.

5.2 Safety Data

Dr. Brugge's safety review of S-026 was based on an integrated database consisting of a pooling of safety data for the three 8-week studies. There was no safety update.

Overall, 735 patients were exposed to Paxil in the sponsor's development program for generalized anxiety disorder. This represented an exposure time on paroxetine of approximately 100 years. Patients in this integrated database were roughly 2/3 female and predominantly white. The mean ages for the 3 studies ranged from 40 to 45 years of age. Seventy-five percent of exposure was in the 11-30 mg/day range, with about 20% having mean doses over 30 mg/day.

Given our prior knowledge of the risks associated with the immediate release Paxil tablet in the same dose range utilized in this program, the focus in the safety review was on any differences between the recognized safety profile for this drug in its approved indications from that observed in the GAD population.

5.2.1 Overview of Adverse Event Profile for Paxil Tablets in GAD

Overall, the adverse events profile for Paxil tablets in GAD was comparable to that observed in patients with depression, OCD, panic disorder, and social anxiety disorder receiving this drug.

5.2.2 Conclusions Regarding Safety of Paxil in GAD

There were no new safety findings to suggest a substantially different safety profile for Paxil tablets in GAD compared to that observed for the other 4 approved indications, and no basis for substantial changes in the labeling for Paxil from the standpoint of safety.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Brugge reviewed the published literature for Paxil in GAD included in the NDA; SKB found only a single reference pertaining to the safety of paroxetine in GAD. This reference did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Paxil is not approved for the treatment of GAD anywhere at this time. We will ask for an update on the regulatory status of Paxil for GAD in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

DSI inspected 1 site from study 641 and 2 sites from study 642. No significant deviations were found. Thus, they recommended that we accept data from these 2 studies.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 4-28-00.

10.2 Foreign Labeling

Paxil is not approved for GAD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update. We will request pediatric studies in the approval letter.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil tablets are effective and acceptably safe in the treatment of GAD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:

Orig NDA 20-031/S-026
HFD-120
HFD-120/TLaughren/RKatz/KBrugge/PAndreason/AMHomonnay

DOC: MEMPXGAD.AE1

/s/

Thomas Laughren
1/28/01 09:51:40 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 5, 2000

TO: Anna Marie Homonnay, R. Ph., Regulatory Project Manager
Karen Brugge, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-031/SE1-026

APPLICANT: SmithKline Beecham Pharmaceuticals

DRUG: Paxil (paroxetine)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Generalized Anxiety Disorder

ACTION GOAL DATE: February 28, 2001

I. BACKGROUND:

Routine clinical inspections were conducted in support of the above-noted application and focused on protocols #641 and #642 by the clinical investigators noted below. Goals of inspections included validation of the primary efficacy endpoint data and subject safety parameters at the sites, along with an analysis of the adequacy of informed consent.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Hartford	Cincinnati	Ohio	August 22, 2000	October 30, 2000	NAI
Khan	Bellevue	Washington	August 22, 2000	September 26, 2000	VAI
Melchor	Miamik	Florida	August 22, 2000	October 11, 2000	NAI

Protocol #641

1. Site #1 (James T. Hartford, M.D. – Cincinnati, Ohio):

Thirty-one (31) subjects were screened, twenty-five (25) of whom enrolled in the study at this site. Eighteen (18) subjects completed the study. Seven (7) subjects discontinued (4 due to adverse events and 3 due to non-compliance).

Records for eight (8) subjects were reviewed, along with informed consent for all subjects. No violations of federal regulations were noted.

Data acceptable

2. Site #2 (Arifulla Khan, M.D. – Bellevue, Washington):

Thirty-two (32) subjects were randomized at this site, twenty-two (22) of whom completed the study. Nine of the ten discontinuations were due to consent withdrawal or loss to follow-up; one was due to a protocol violation. Inspection found adequate documentation of attempts to contact those lost to follow-up. No under-reporting of adverse events was noted.

Records for seventeen (17) subjects were reviewed, along with informed consent for all subjects. A Form FDA 483 was issued for three protocol deviations and several recordkeeping deficiencies, none of which adversely impact data acceptability.

In addition to the above findings, the following sponsor/site discrepancies have been noted in review of the establishment inspection report: Data provided by the sponsor indicate that 28 subjects were randomized, whereas the site's enrollment log indicates that 32 subjects were randomized. In addition, sponsor-provided data indicate that 6 subjects were discontinued after randomization, while the site's enrollment log shows that 10 subjects were actually discontinued post-randomization.

Data acceptable

Protocol #642

Site of Pedro Melchor, M.D. – Miami, Florida:

Twenty-four (24) subjects were enrolled at this site, four (4) of whom discontinued (3 due to non-serious adverse events, 1 lost to follow-up). Records were reviewed for twelve (12) subjects, along with informed consent for all subjects. No violations of federal regulations were noted.

Data acceptable

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Clinical inspections in support of pending NDA 20-031/SE1-026 focused on the conduct of protocol #641 by Drs. James T. Hartford and Arifulla Khan and on the conduct of protocol #642 by Dr. Pedro Melchor. None of the inspectional observations noted during inspection of Dr. Arifulla Khan appear to affect the reliability of the data from that site. Inspection of Drs. Hartford and Melchor found that they conducted protocols #641 and #642, respectively, in accordance with pertinent federal regulations. Accordingly, it is recommended that the data submitted by these clinical investigators may be used in support of pending NDA 20-031/SE1-026.

Key to Classification:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAI-r = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

/S/

Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
NDA 20-031
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Hajarian/Lewin
HFD-47/GCP IIBranch Chief
HFD-47/Kline for GCPB File #####
HFD-47/Reading File

Date: 8/7/00
Re: NDA 20-031/S-026
Indication: Generalized Anxiety Disorder
From: Karen Brugge, M.D. and Paul Andreason, M.D.

The subjects described below with abnormal laboratory values met the criteria for "Potential Clinical Concern" (PCC). Please provide any additional information that may be helpful in clarifying some areas of uncertainty, as described below:

1. **Subject 637.099.03820**: This 58 y.o. subject, with Parkinson's disease, had an abnormal baseline laboratory value for TSH of 0.1 mU/l (normal reference range: 4.0-5.5mU/l). This subject's white blood cell count dropped from 6.3 $x10^{9th}$ cells/l at baseline to $2.2x10^{9th}$ cells/l after 54 treatment days (week 8 visit). At 54 days of treatment, eosinophil and monocyte levels (17% and 15%, respectively) were high but reported to be within the normal range at baseline. These abnormal laboratory values met PCC criteria, but were not reported to be associated with any AE's. Given the Parkinson's disease and low TSH level, it is not clear why this patient was included in the study and what the follow-up was for the abnormal laboratory results.

2. **Subject 641.115.00708A**: This 74 y.o. year old subject, with a history of breast cancer, had low free T3 levels and thrombocytopenia at screening with a platelet count of 96 $x10^{9th}$ cells/l (normal: 130-400 $x10^{9th}$ cells/l). Her white cell blood cell count at both screening and on study visit week 8 were also low with 3.0 $x10^{9th}$ cells/l and 2.0 $x10^{9th}$ cells/l, respectively, which met PCC criteria. According to the narratives for this subject, no AE's were associated with low white cell counts. A pre-existing low white count suggests that this abnormal laboratory parameter was not likely to be drug-related. It is not clear why this subject was included or what her condition and laboratory status was at follow up.

3. **Subject 641.118.00851**: This subject was a 63 y.o. Indian male with a history of multiple fractures, removal of his right patella, and current history of hyperlipidemia and hypertension for which he was receiving Lipitor and Zestril, respectively. An adverse dropout was reported with a slightly elevated eosinophil count at baseline (9% compared to 0-7% range for within normal limits) and of 13% on Day 56, the latter which met PCC criteria. This subject also had a mildly elevated alkaline phosphatase level on Day 56 (132.0 IU/l). The reported adverse events that led to cessation of paroxetine treatment on Day 11 were ataxia, dizziness, dyspepsia, palpitation and somnolence. The events resolved within at least 13 days. There was no indication of the duration of the abnormal laboratory values.

4. **Subject 637.062.03804**: This subject was a 29 y.o. healthy WF on no concomitant medications and whose laboratory values were within normal limits at screening. On Day 54 of treatment (in the 50 mg paroxetine group) she had a markedly elevated creatinine of 645umol/l (normal range: 44-124 umol/l) and a potassium of 7.5umol/l, (normal range: 3.5-5.3 umol/l). BUN was mildly elevated from 10.3 at baseline to 11.4 umol/l on Day 54 (normal range 2.5-9.0 umol/l). The narrative for this subject indicated that the "patient completed the study as planned" and that "no further data are available". Therefore, results of a diagnostic work-up, follow-up, resolution, and treatment of these abnormal findings remain unclear.

5. **Subject 641.133.01610**: This subject was a 40 y.o. Hispanic male with a history of enlarged prostate who also exhibited marked elevation of creatinine levels from 88.4 umol/l (within normal limits) at baseline to 353.6 umol/l on Day 56 of treatment. This subject also had a mildly elevated ALT level of 93 IU/l (normal 0-48)which did not meet PCC criteria. The investigator reported the elevated creatinine as a negative adverse event and the patient was described as having "completed the study as planned". It is not clear why this subject was included in the study, given the abnormal baseline creatinine level and what the work-up, diagnosis and follow-up was for this patient.

6. **Subject 641.132.01559:** This subject was a 30 y.o. WF who showed a marked increase in creatinine and BUN from baseline levels of 88.4 umol/l and 3.6 mmol/l, respectively, to levels of 265.2 umol/l and 14.3 mmol/l, respectively, on Day 60 of treatment. The potassium level of this patient was also increased from baseline (within normal limits) to Day 60 of treatment to 6.0 mmol/l (normal: 3.5-5.3 mmol/l). The narrative indicates that the baseline WBC was elevated at $13x10^{9th}$ cells/l (normal limits: 3.8-10.8) and the subject had a history of bronchitis and was being treated with Biaxin for a "throat infection". Other concomitant medications included Percocet, Relafen, Triple Lesitan and Keflex (for carbuncles). The patient also had a history of gastritis, laparoscopy (exploratory), benign breast cyst and migraine. The patient was reported to have completed the study as planned. The work-up diagnosis, follow-up, resolution and treatment of these abnormal findings are unclear.

7. **Subject 641.146.0229**: This subject was a 22 y.o. Asian female with no reported AE's. This subject showed a marked increase in potassium from baseline at 4.0 mmol/l (within normal limits) to Day 59 of treatment (8.0 mmol/l). The narrative does not indicate if any AE's were associated with this laboratory finding or follow-up status. The diagnostic work-up and diagnosis of this abnormal laboratory value is unclear.

8. **Subjects 637.055.03668, 637.099.03849, 641.131.01517, 641.121.01002:** These four subjects were from the paroxetine groups and met PCC criteria for high bilirubin levels on Day 42 to 56 of treatment onset. They also had abnormal bililrubin levels at baseline, some of which met PCC criteria at baseline. It is not clear why these subjects were included in the study.

9. **Subjects 637.058.03692 and 637.058.03720**: These two subjects had elevated bilurubin levels of 35 umol/l (0-22 umol/l within normal limits) meeting PCC criteria on Days 10 and 58, respectively. After treatment onset of paroxetine, baseline levels were within normal limits (20 and 10 umol/l, respectively. The former subject dropped out of the study on day 3 after he experienced an "allergic reaction" for 2 days which was treated with Zyrtec®. The abnormal bilirubin level meeting PCC criteria was observed on Day 10 (7 days later) along with slightly elevated AST and ALT levels that did not meet PCC criteria. No follow-up or pertinent details could be found in the narrative or in the CRF on this subject.

10. **Subject (637.058.03720)**: This subject was a 42 y.o. WM with an abnormal bilirubin level on Day 58 with a medical history that included back pain and a past history of herniated disc. He experienced "moderate back pain" on Day 54 of paroxetine treatment (4 days before his blood chemistries were drawn). It is not clear where the back pain was located (i.e. whether it was right sided in an area suggestive of referred pain from the liver or gall bladder versus located near the area of previously experienced pain associated with a past herniated disc). The back pain lasted 3 days and was treated with Myolastan® (a benzodiazapine) and Voltaran® (an NSAID). Amylase and/or SGGT levels were not reported to have been drawn and no other symptoms/signs were described in the narrative.

11. **Subject 637.018.03330:** met the criterion for low systolic blood pressure (89 mmHg after Day 7 from the start date of the study drug, with baseline systolic BP of 100 mmHg). This 75 year old male had current history of diabetes mellitus, congestive heart disease among other illnesses. He developed "severe vomiting" on Day 1 of treatment which lasted 4 days, resulting in withdrawal from the study. It is not clear if the low blood pressure was associated with dehydration, an exacerbation of the patient's underlying congestive heart disease or some other cause. Information regarding a diagnostic work-up, follow-up and treatment cannot be found in the submission. Given the patient's congestive heart disease at baseline, it is also not clear why this patient was included in the study.

6/29/00
To: Assistant Director Thomas Kline
US Regulatory Affairs, SmithKline Beecham
Fax: 610/917-7665
From: Karen Brugge, M.D. and Paul Andreason, M.D
Medical Officers, CDER, FDA
Re: sNDA 20-031

|S|

Thank you for speaking with us on the telephone today. Per our discussion:

- According to the submission approximately 7 to 9% of subjects in each treatment group of Study 637 had Parkinson's disease with a similar percentage of subjects receiving dopamine agonists. Therefore, the screening of subjects in the European study (Study 637) does not seem to reflect the methods described in the protocol of the sponsor's submission. The submission indicates that patients with the following clinically findings were to be excluded from the study: "clinically significant abnormalities on ... or physical examination at screening which had not resolved prior to the baseline visit", or with "clinically significant condition which in the opinion of the investigator would have rendered the patient unsuitable for the study...". Hence, our questions regarding the above are the following:
  - **a.** Why were Parkinson's patients included in Study 637 ?
  - **b.** Are the screening methods accurately described in the submission?
- Would you please provide a copy of the HAD scale with the items numbered so that we may confirm which items were used for the Anxiety and Depression subscale.

Thank you for considering the above and we look forward to your response.

Cc: Annemarie Homonnay, CSO

MODE = MEMORY TRANSMISSION START=JUN-12 15:02 END=JUN-12 15:07

FILE NO.= 104

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	s	916109177665	001/001	00:00'16"

-FDA/DNDP -

********** - - ***** - 3015942859- **********

Attn: Thomas Kline, Assistant Director of Regulatory Affairs
Smith Kline Beechum
Fax: 610/917-7665
From: Karen Brugge, M.D. and Paul Andreason, M.D., CDER Medical Reviewers, FDA
Date: 6/12/00

Thank you for our telephone conversation today. As we discussed, please provide the following for each of the 3 completed studies (#637, 641, 642) by June 16, 2000:

- Line Listing of each of the following:
  - Serious Adverse Events (SAE)
  - Adverse Dropouts
  - All patients meeting criteria for "Potential Clinical Concern" (PCC) for Clinical Laboratory Tests, Vital Sign parameters and Weight. Also provide PCC criteria for urinalysis measures and provide line listing for those meeting PCC criteria.
  - Adverse dropouts due to PCC as a separate listing
  - Adverse dropouts due to an abnormal safety assessment (e.g. abnormal laboratory values) as a separate listing

Please include patient identification number, preferred term, verbatim term and location of the narrative (case summary). Please include baseline measures and follow-up measures regarding patients in the above line listings with safety assessments (e.g. laboratory measures, vital sign parameters, etc.) that were the reason for the SAE, Adverse dropout or the reason for meeting PCC criteria.

- Although the submission describes adverse dropouts and SAE's due to meeting PCC for various safety assessments (including urinalysis results) the actual numbers were not provided in all sections. Please provide these numbers for each of the safety assessments in each of the three completed studies. Also provide outcome of patients with abnormal urinalysis such as hematuria.
- Please provide an adverse event thesaurus

Please do not hesitate to contact me regarding questions or problems regarding the above at 301/594-5540.

Cc. CSO Annemarie Homonnay - FYI re: sNDA 20-031