

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75049

ADMINISTRATIVE DOCUMENTS

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: August 2, 2001

FROM: Gary J. Buehler ✓ |S| 8/2/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: ANDA 75-049
Fluoxetine Hydrochloride Capsules
Geneva Pharmaceuticals, Inc.

TO: The Record Regarding U.S. Patent No. 6,258,853

July 10, 2001, U.S. Patent No. 6,258,853 (the '853 patent) was issued to Stowell, et.al. The abstract of the patent states "The present invention relates to novel pharmaceutical formulations and methods of using Form A of fluoxetine hydrochloride".

On July 18, 2001, aai Pharma (aai) submitted a letter to the Agency under 21 C.F.R. 314.53(f) to advise the agency that the holder of NDA 18-936, Eli Lilly & Co. (Lilly) for Prozac® (fluoxetine hydrochloride) has failed to submit required patent information under 21 U.S.C. 355(c)(2) with respect to the '853 patent. aai claims that the patent meets all the legal requirements for listing and that Lilly must list the patent in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). aai requested that FDA contact Lilly to confirm the correctness of Lilly's omission of information with respect to the '853 patent. aai also stated that FDA has an obligation to effect the Congressional intent of protecting patent owner rights whether or not the patent owner or licensee is an NDA applicant.

On July 23, 2001, the FDA issued a letter to Lilly asking Lilly to review the patent challenge submitted under 314.53(f) and to confirm whether the patent information for NDA 18-936 was correct.

On July 31, 2001, Lilly replied to the FDA's July 23, 2001, letter and stated they reviewed the challenge and that the patent

information contained in the Orange Book is correct. Lilly stated that no changes need to be made to the patent and exclusivity information addendum of the Orange Book.

On August 2, ~~2001~~, the Agency fully approved applications for fluoxetine hydrochloride that were otherwise ready for approval. All scientific and regulatory issues had been resolved. All patent and exclusivity information currently listed in the Orange Book had been addressed.

The statute 21 U.S.C. 355(c)(2) states that the holder of an approved application shall file with the Secretary, the patent number and the expiration date of any patent which claims the drug for which the application was submitted, or which claims a method of using such drug, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. Because the NDA holder, Lilly, declined to list the '853 patent, the Agency did not list the patent. The Agency's ministerial role in the patent listing process is limited. The statute requires the Agency to publish the patent after it is submitted to the Agency by the applicant. The Agency does not independently list patents, which are not submitted to it by the applicant for listing. The Agency fulfilled its ministerial role by forwarding the patent challenge submitted under 21 C.F.R. 314.53(f) for the '853 patent to the NDA applicant, Lilly.

Superseded by TA
Summary dated
9/27/99

**TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: , 75-049 Date of Submission: September 22, 1998

Applicant's Name: Geneva Pharmaceuticals, Inc.

Established Name: Fluoxetine Capsules USP, 10 mg and 20 mg

APPROVAL SUMMARY:

PLEASE NOTE THAT IF THIS DRUG PRODUCT IS TO BE APPROVED BEFORE NOVEMBER 21, 1999 THE INSERT LABELING MUST BE REVISED TO DELETE THE INFORMATION CONCERNING THE TREATMENT OF BULIMIA.

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 10 mg and 20 mg (100s)
Satisfactory as of August 12, 1998 submission.

Unit Dose Blister Labels: 10 mg and 20 mg
Satisfactory as of September 22, 1998 submission.

Unit Dose Carton Labeling 10 mg and 20 mg (100s)
Satisfactory as of September 22, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of August 12, 1998 submission.

Revisions needed post-approval: NONE

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac®

NDA Number: 18-936 NDA Drug Name: Prozac®

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 3/13/98 (S-051)

Has this been verified by the MIS system for the NDA? Yes
 Was this approval based upon an OGD labeling guidance? No
 Basis of Approval for the Container Labels: side by sides

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book? *	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	

	Yes	No	N.A.
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

FOR THE RECORD: (portions taken from previous review)

1. The model insert for this review is Prozac®, Lilly Research Laboratories, NDA 18-936/S-051 approved on 3/13/98 in draft. There was a guidance dated 6/92, which is out of date. However, it was utilized to identify the locations for the salt form of the established name.
2. As of the 7th supplement of USP 23, Fluoxetine Capsules has a monograph and so this is the established name [Fluoxetine Capsules].

3. Patent/Exclusivities:

Two patents are still in effect for the innovator. No. 4626549 for a method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) expires December 2, 2003. The other patent, No. 4314081, is for the chemical entity itself, per Mary Ann Holovac at HFD-85, and expires February 2, 2001. Geneva will not market this product until 2003. There is a generic firm call Barr who is pursuing 505(j) (2) (B) of the Act and will give notice to the innovator that the patents are invalid, unenforceable, or will not be infringed on by the manufacture, use, or sale of Fluoxetine Hydrochloride Capsules.

As of a May 21, 1997 submission, Geneva is claiming that U.S. patent, No. 4314081, is invalid or will not be infringed by the manufacture, use, or sale of the fluoxetine hydrochloride 10 and 20 mg capsules for which this application is submitted.

In addition, I-166 (treatment of bulimia) & U-154 (Method of treating animals suffering from an appetite disorder - [NOT APPLICABLE]) both expire 11/21/99. Since the patent for prozac expires in 2001 and the treatment of bulimia expires before that time, we asked the firm to revise labeling according to the approved labeling cited above. This labeling contains significant changes in addition to the treatment for bulimia.

With the October 6, 1997 amendment Geneva certifies that they will remove the information concerning the treatment of bulimia if this drug product is approved before 11/21/99.

There is exclusivity for the treatment of obsessive-compulsive disorder (I-102) which expired February 28, 1997. Geneva includes this information.

The August 12, 1998 amendment provides for the addition of unit-dose packaging and the September 22, 1998 amendment provides for the revision of this labeling.

4. Product Line:

The innovator markets their product as follows:
10 mg capsules in bottles of 100 and "flexible blister" cards of 31 in cartons of 20; 20 mg capsules in 30s, 100s, unit dose 100s, and flexible blisters of 31s in cartons of 20; oral solution, 20 mg/5 mL in 120 mL containers.

The applicant proposes to market their 10 mg and 20 mg capsules in bottles of 100 and UD cartons of 100s.

5. Dispensing Recommendations:

NDA - No statement for capsules. Combined insert has a statement for the oral solution.

ANDA - Dispense in ... tight, light-resistant container. Keep tightly closed.

USP - Preserve in tight, light-resistant containers.

6. Storage Conditions:

NDA - Store at CRT 15°-30°C (59°-86°F)

ANDA - Store at CRT 15°-30°C (59°-86°F)
 UD carton - Protect from moisture.

7. The insert contains information regarding the effect of food on absorption. A fasting and non-fasting study has been done. The bio has been found acceptable. The waiver for in vivo bioequivalency of the 10 mg capsule was granted.

8. The DESCRIPTION section is consistent with the composition statement on page 60 (v 1.1).

Date of Review: 9/28/98

Date of Submission: 9/22/98

Primary Reviewer: Adolph Vezza

Date:

9/29/98

Team Leader: Charlie Hoppe

Date:

9/29/98

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