Summary Report

Fluoxetine hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Prepared by:

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of fluoxetine hydrochloride (fluoxetine HCl; UNII code: I9W7N6B1KJ), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how fluoxetine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how fluoxetine HCl has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of fluoxetine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Fluoxetine HCl was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc for depression, anxiety, and separation anxiety via 10-50 mg/mL topical preparations (gels and creams), 2-10 mg/mL oral preparations (solutions and suspensions), and oral capsules.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of fluoxetine HCl.[6-10]

Reasons provided for nomination to the 503B Bulks List included:

- Capsules/tablets are not appropriate for compounding transdermal veterinary preparations. They interfere with the pharmaceutical elegance of the finished compounded preparation.
- Patient intolerance to inactive ingredients and/or excipients found in FDA-approved products.

Triangle Compounding Pharmacy, Inc was contacted to clarify their nomination for topical fluoxetine preparations. They reviewed their compounding history over the past 6 years and determined that all topical preparations during that time period were made for animals. Therefore, topical preparations were not considered for this report.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of fluoxetine HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for fluoxetine HCl; name variations of fluoxetine HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing fluoxetine HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Fluoxetine HCl is a component of an FDA-approved product. The nominated oral compounded products did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances fluoxetine HCl was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use fluoxetine HCl: primary care and internal medicine and psychiatry. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of fluoxetine HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Fluoxetine HCl is available as an FDA-approved product in the nominated dosage form and ROA.
- Fluoxetine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for fluoxetine HCl.
- Fluoxetine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Fluoxetine HCl	10-40 mg	Capsule	Oral	Prescription	12/29/1987
Fluoxetine HCl	90 mg	Delayed release capsule	Oral	Prescription	3/22/2010
Fluoxetine HCl	20 mg/5 mL	Solution	Oral	Prescription	8/2/2001

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Fluoxetine HCl	10-60 mg	Capsule, tablet	Oral	Abu Dhabi	Active	–
				Australia	Prescription	9/5/1991
				Belgium	Prescription	9/16/1986

				Canada	Prescription	12/31/1989
				Hong Kong	Prescription	6/25/1988
				Ireland	Pharmacy-only[c]	2/19/1999
				Latvia	Prescription	11/6/2002
				Namibia	–	12/31/1986
				New Zealand	Prescription	2/4/1988
				Saudi Arabia	Prescription	–
				UK	Prescription	8/6/1999
Fluoxetine HCl	20 mg/5mL	Solution	Oral	Abu Dhabi	Active	–
				Australia	Prescription	7/13/1993
				Canada	Prescription	6/16/1997
				Ireland	Pharmacy-only[c]	2/23/1994
				New Zealand	Prescription	10/7/2010
				UK	Prescription	6/24/2002

Abbreviation: "– ", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

No literature review was conducted.

Characteristics of included studies

No literature review was conducted.

Use of fluoxetine HCl

No literature review was conducted.

Pharmacology and historical use

No additional references were found that provided information about the pharmacology or historical use of fluoxetine HCl.

Table 3. Types of studies

No literature review was conducted.

Table 4. Number of studies by country

No literature review was conducted.

Table 5. Summary of included studies

No literature review was conducted.

Table 6. Dosage by indication – US

No literature review was conducted.

Table 7. Dosage by indication – non-US countries

No literature review was conducted.

Table 8. Number of studies by combination

No literature review was conducted.

Table 9. Compounded products – US

No literature review was conducted.

Table 10. Compounded products – non-US countries

No literature review was conducted.

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Six SMEs discussed fluoxetine HCl. Amongst these 6 SMEs, there were 5 medical doctors and 1 pharmacist. The SMEs specialized and/or were board-certified in child and adolescent psychiatry, primary care and family practice, and psychiatry, working in academia and academic medical centers. The SMEs had been in practice for 10 to 30 years.

Prozac® (fluoxetine) is indication for treatment of depression. In pediatrics, escitalopram and fluoxetine are the only two antidepressants that are FDA-approved. Fluoxetine is one of the most studied antidepressants in children.

According to the SMEs, the commercially available fluoxetine products are sufficient. One SME remarked that they give fluoxetine in every formulation they can find, mostly as an oral tablet. The SMEs had never encountered a patient with allergies to the inactive ingredients. If children are unable to swallow pills, then fluoxetine is available as a liquid formulation and there are techniques to teaching them how to swallow pills. Fluoxetine has a very long half-life, and this can be helpful for medication adherence in younger patients. Several SMEs stated that having lower concentrations of fluoxetine solutions available could be useful for dose titration or tapering in patients, especially children. One SME mentioned that fluoxetine is hard to discontinue due to the body's withdrawal response (i.e. dizziness and irritability) when doses are missed. Most SMEs were not familiar with administering fluoxetine topically; one SME commented that the topical product is used in animals.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which fluoxetine HCl prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded fluoxetine HCl

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded fluoxetine HCl

No respondents to survey distributed via professional medical associations

CONCLUSION

Fluoxetine HCl was nominated for inclusion on the 503B Bulks List for depression, anxiety, and separation anxiety via 10-50 mg/mL topical preparations (gels and creams), 2-10 mg/mL oral preparations (solutions and suspensions), and oral capsules. Fluoxetine HCl is available as an FDA-approved product as an oral capsule and solution; it is also available in the nominated dosage forms and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

No literature review was conducted.

From the interviews, fluoxetine is used for treatment of depression. Most SMEs did not see a need for additional forms of fluoxetine as the commercially available fluoxetine products met their prescribing needs, although they did express an interest in lower concentration fluoxetine solutions for dose titration or tapering. The topical fluoxetine formulation is used in animals.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

REFERENCES

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

No literature review was conducted.

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded fluoxetine HCl. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer fluoxetine HCl to your patients?

   - o Yes
   - o No

3. I prescribe or administer fluoxetine HCl for the following conditions or diseases: (check all that apply)

   - o Anxiety
   - o Depression
   - o Other (please explain) _____

4. I use fluoxetine HCl with my patients as the following: (check all that apply)

   - o FDA-approved drug product
   - o Compounded drug product
   - o Over-the-counter drug product
   - o Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
   - o Other (please describe) _____

5. I use compounded fluoxetine HCl because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain)_____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing fluoxetine HCl.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded fluoxetine HCl at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded fluoxetine HCl from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.