CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA 021164 Executive Summary Assessment 4

1. Application/Product Information

NDA Number.	021164		
Applicant Name	Fabre-Kramer Pharmaceuticals, Inc.		
Drug Product Name	gepirone hydrochloride		
Dosage Form.	Tablet, extended release		
Proposed Strength(s)	20 mg, 40 mg, 60 mg, 80 mg		
Route of Administration	Oral		
Maximum Daily Dose	80 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Major Depressive Disorder (MDD)		
Drug Product Description	Pink, off-white, yellow or red-brown rectangular shaped tablet, debossed with “FK” on one side and 1, 7, 11 or 17 on the other		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°–25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katharine Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Venkat Pavuluri	Valerie Amspacher
	Manufacturing	Tarun Mehta	Sridhar Thumma
	Biopharmaceutics	Kalpana Paudel	Okponanabofa Eradiri

	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Teshara Bouie	
	ATL	Valerie Amspacher	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 48 months is acceptable when stored at 20°–25°C (68°–77° F).

b. Additional Comments for Action – N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation is approval for this application based on reviews from drug substance, drug product, process/facilities and biopharmaceutics. This NDA was submitted previously in 1999 and determined to be not approvable in 2002.

It was resubmitted Dec 2003 and determined to be not approvable Jun 2004. It was resubmitted May 2007 and determined to be not approvable Nov 2007. This review is of the resubmission dated 23 Dec 2022.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate

Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 71; eCTD 0005	23 Dec 2022	All, original submission
Supporting document 72; eCTD 0006	17 Jan 2023	Facilities
Supporting document 80; eCTD 0014	11 Apr 2023	Process/facilities
Supporting document 82; eCTD 0016	19 Apr 2023	Biopharmaceutics
Supporting document 86; eCTD 0020	28 Apr 2023	Drug product
Supporting document 88; eCTD 0022	2 May 2023	Drug product
Supporting document 89; eCTD 0023	4 May 2023	Drug product
Supporting document 90; eCTD 0024	9 May 2023	Drug product
Supporting document 95; eCTD 0029	19 May 2023	Drug product
Supporting document 99; eCTD 0033	14 Jun 2023	Drug product
Supporting document 102; eCTD 0036	29 Jun 2023	Drug product
Supporting document 103; eCTD 0037	30 Jun 2023	Drug product

Supporting document 105; eCTD 0039	11 Jul 2023	Drug substance, drug product
Supporting document 109; eCTD 0043	14 Aug 2023	Drug product
Supporting document 110; eCTD 0044	22 Aug 2023	Drug product
Supporting document 112; eCTD 0047	24 Aug 2023	Drug product
Supporting document 113; eCTD 0046	24 Aug 23	Drug product

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: as submitted in eCTD SN 0013, dated 07-APR-2023

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	*Comment to Applicant: Revise established name as "gepirone" in the product title. The product tile should be "EXXUA*

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

		(gepirone) extended-release tablets, for oral use"
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Comment to Applicant*: Revise the sentences as "Extended-release tablets: 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg". Revise the dose expressions to "gepirone" equivalent quantities (i.e., 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg) throughout the Prescribing Information deleting the current whole numbers (i.e., 20 mg, 40 mg, 60 mg, and 80 mg).*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	Same as above comment to Applicant*: Revise the sentences as "Extended-release tablets: 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg.*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	Oral extended-release solid dosage form to be taken as whole unit, doesn't require preparation or reconstitution prior to administration.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	The tablets should not be broken, crushed, chewed, or dissolved.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	

Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

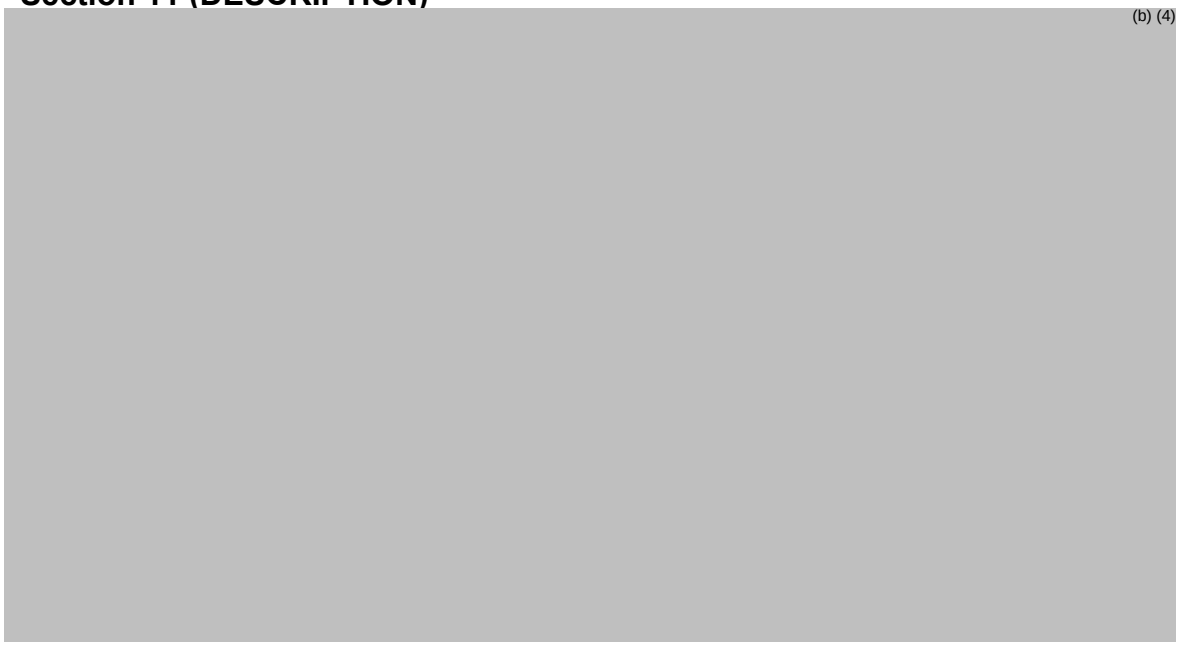
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	Comment to Applicant*: Revise the statement "EXXUA is available as extended-release tablets in the following strengths" to "EXXUA is available as extended-release tablets in the following strengths, as gepirone base".*
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Comment to Applicant: *Revise the sentences for each of the strength to include the identifying characteristics of the dosage form, i.e., shape of the tablets, required per 21 CFR 201.57(b)(4)(ii); e.g., 18.2 mg: pink, modified rectangular, with "FK" debossed on one side and "1" on the other side.*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	*Comment to Applicant: Revise the 1st sentence in 'Description' section as "EXXUA contains gepirone, in the salt form gepirone hydrochloride (HCl)" abbreviating the salt form 'hydrochloride' a first occurrence with (HCl) in parenthesis.*
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	*Revise the second sentence in the 3rd paragraph of 'Description' section of PI as "Each extended-release tablet contains 18.2 mg, 36.3 mg, 54.5 mg, or 72.6 mg of gepirone equivalent to 20 mg, 40 mg, 60 mg, or 80 mg, of gepirone HCl respectively."*
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Pharmacological class of the drug was not defined anywhere in the PI (b) (4) by the division during the labeling review.
Chemical name, structural formula, molecular weight	Adequate	

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	Comment to Applicant: *The words "(b) (4)" shall be removed from first sentence in 3rd paragraph. Also, delete (b) (4) from last sentence of the paragraph 3.*
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	Comment to Applicant: *Revise the first sentence as "EXXUA ER tablets are supplied in bottles of 100 with child resistant cap and in four dosage strengths as:"*
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures'" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Comment to Applicant: *Revise the 1st sentence under Storage as "Store at 20°C to 25°C (68°F to 77° F); excursions are permitted to 15°C to 30°C (59°F to 86°F)."*
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	*Comment to Applicant: Revise the first sentence under "HOW SUPPLIED/STORAGE AND HANDLING" section of PI as "EXXUA (gepirone) extended-release tablets are supplied in bottles of 100*

		with child resistant cap and in four dosage strengths:",

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Comment to Applicant*: Move the Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer, currently at the end of section 16, to end of section 17.*

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Medication Guide

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Inadequate	*Comment to Applicant: Include established name of the drug product "EXXUA (gepirone) extended-release tablets, for oral use" under the title 'Medication Guide'.*
Special preparation instructions (If applicable)	Adequate	Swallow EXXUA tablets whole. Do not break, chew, crush, or dissolve tablets.
Storage and handling information (If applicable)	Inadequate	*Comment to Applicant: Revise the section 'How should I store EXXUA?' as:* • *Store at 20°C to 25°C (68°F to 77°F);* (b) (4) • *Protect from high humidity and moisture.* • (b) (4) • *Keep EXXUA and all medicines out of the reach of children.*
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	
Active ingredient(s) (if applicable)	Inadequate	*Comment to Applicant: Revise active ingredient name to gepirone, deleting the "HCl" under 'What are the ingredients in EXXUA?'.*
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Inadequate	*Comment to Applicant: Include Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.*

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING (As submitted in eCTD SN 0042, dated 31-JUL-2023)

Reviewer Note: In response to Agency's request for information (RFI) Applicant proposed to withdraw (b) (4) (RFI response in eCTD SN 0024, dated 09-MAY-2023) that was initially proposed for (b) (4) Applicant also agreed to correct the typographical errors of (b) (4) in Table 3.2.P.7.1 Drug Product container closure system, and in Module 3.2.P.8.1, in text describing Table 3.2.P.8-1. In response to another RFI dated 10-MAY-2023, Applicant also agreed to follow and abide by (b) (4)

3.1 Container Labels

Start of Applicant material

(b) (4)

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

(b) (4)

End of Application material

3.2 Carton Labeling

Not Applicable, only bottle label provided.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton/Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Inadequate	*Comment to Applicant: Revise established name to "gepirone"*, [i.e., *EXXUA (gepirone) extended-release tablets]*
Strength(s) in metric system	Inadequate	*Comment to Applicant: Revise the product strengths from 20 mg, 40 mg, 60 mg, and 80 mg to 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg respectively* (b) (4)
Route(s) of administration	Adequate	Oral products are exempt from this requirement.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Inadequate	*Comment to Applicant: Revise the statement "Each tablet contains: XX mg of Gepirone HCL, USP equivalent to YY mg of Gepirone" on all labels to "Each extended-release tablet contains XX mg gepirone equivalent to YY mg gepirone hydrochloride". Also remove the reference to USP on all labeling materials, in reference to gepirone or gepirone hydrochloride which doesn't have USP monographs.*
Net contents (e.g., tablet count, volume of liquid)	Inadequate	*Comment to Applicant: The net content "100 tablets" may be relocated to another place, away from product strength, on principal panel for all retail packs. Also note* (b) (4) *, following our request for information dated 5/10/2023 advising you to* (b) (4)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Inadequate	*Comments to Applicant:* *- Add a place holder for Lot number and expiration date on all container labels.* *- Provide an identifying lot number from which it is possible to determine the complete manufacturing history of the package of the drug, required per 21 FR 201.100(b)(6).* *- Identify the expiration date format you intend to use. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.*
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	*Comment to Applicant: Revise the storage statements as: Store at 20°C to 25°C (68°F to 77° F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from high humidity and moisture.*
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton / Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Inadequate.

ITEMS FOR ADDITIONAL ASSESSMENT

A. Prescribing Information (PI) and Medication Guide (MG):

HIGHLIGHTS OF PRESCRIBING INFORMATION:

1. *Revise established name as "gepirone" in the product title. The product tile should be "EXXUA (gepirone) extended-release tablets, for oral use"*
2. *Revise the statement under "Dosage Forms and Strengths" in Highlights section of PI as "Extended-release tablets: 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg. Revise the dose expressions to "gepirone" equivalent quantities (i.e., 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg) throughout the Prescribing*

Information deleting the current whole numbers (i.e., 20 mg, 40 mg, 60 mg, and 80 mg).

Full Prescribing Information

Section 2 (DOSAGE AND ADMINISTRATION):

3. *Revise the dose expressions to "gepirone" equivalent quantities (i.e., 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg) as applicable, deleting the current whole numbers (i.e., 20 mg, 40 mg, 60 mg, and 80 mg) that are equivalents to "gepirone HCl" quantity in respective gepirone ER tablets.*

Section 3 (DOSAGE FORMS AND STRENGTHS):

4. *Revise the statement 1st statement "EXXUA is available as extended-release tablets in the following strengths" to "EXXUA is available as extended-release tablets in the following strengths, as gepirone base".*
5. *Revise the sentences for each of the strength to include the identifying characteristics of the dosage form, i.e., shape of the tablets, required per 21 CFR 201.57(b)(4)(ii); e.g., 18.2 mg: pink, modified rectangular, with "FK" debossed on one side and "1" on the other side.*

Section 11 (DESCRIPTION):

6. *Revise the 1st sentence in 'Description' section as "EXXUA contains gepirone, in the salt form gepirone hydrochloride (HCl)" abbreviating the salt form 'hydrochloride' a first occurrence with (HCl) in parenthesis. The words "(b) (4)" shall also be removed from first sentence in 3rd paragraph.*
7. *Revise the second sentence in the 3rd paragraph of 'Description' section of PI as "Each extended-release tablet contains 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg of gepirone equivalent to 20 mg, 40 mg, 60 mg, and 80 mg, respectively of the gepirone HCl respectively.*
8. *Also, delete (b) (4) from last sentence of the paragraph 3.*

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING):

9. *Revise the first sentence under "HOW SUPPLIED/STORAGE AND HANDLING" section of PI as "EXXUA ER tablets are supplied in bottles of 100 with child resistant cap and in four dosage strengths as:"*
10. *Revise the 1st sentence under Storage as "Store at 20°C to 25°C (68°F to 77° F); excursions are permitted to 15°C to 30°C (59°F to 86°F)."*

Below Section 17 of PI:

11. *Move the Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer, currently at the end of section 16, to end of section 17.*

B. Medication Guide

12. *Include Established name of the drug product e.g., EXXUA (gepirone) extended-release Tablets, for oral use, under the title 'Medication Guide'.*
13. *Revise active ingredient name to gepirone, deleting the "HCl" under 'What are the ingredients in EXXUA?'.*
14. *Revise the section "How should I store EXXUA?" of the Medication Guide to read as:*
    - *Store at 20°C to 25°C (68°F to 77°F);* (b) (4)
    - *Protect from high humidity and moisture.*
    - (b) (4)
    - *Keep EXXUA and all medicines out of the reach of children.*
15. *Include the Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.*

C. Container Labels:

16. *Revise established name to "gepirone", [i.e., EXXUA (gepirone) extended-release tablets].*
17. *Revise the product strengths from 20 mg, 40 mg, 60 mg, and 80 mg to 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg respectively* (b) (4)
18. *Revise the statement "Each tablet contains: XX mg of Gepirone HCL, USP equivalent to YY mg of Gepirone" on all container closure labels to "Each extended-release tablet contains XX mg gepirone equivalent to YY mg gepirone hydrochloride". Also remove the reference to USP in all labeling materials, in reference to gepirone or gepirone hydrochloride which doesn't have USP monographs.*
19. *The net content "100 tables" may be relocated to another place, away from product strength, on principal panel for all retail and sample packs. Also note* (b) (4) *following your response to Agency's request for information dated 5/10/2023 advising you to* (b) (4)
20. *Add a place holder for Lot number and expiration date on all container labels.*
21. *Provide format of lot number to be used for commercial batches. The assigned lot number shall comply with the requirements of 21 FR 201.100(b)(6), i.e., provide the complete manufacturing history of the package of the drug.*
22. *Identify the expiration date format you intend to use. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical*

characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

23. *Revise the storage statements on all container labels as: Store at 20°C to 25°C (68°F to 77° F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from high humidity and moisture.*

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective until the remaining deficiencies delineated in the List of Deficiencies (for PI, Med. Guide, IFU and Carton and container labels) above are satisfactorily resolved. The above deficiencies will be resolved by sending request for information and through labeling negotiation with Applicant prior to final approval.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, PhD, R. Ph.; 16-AUG-2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Valerie Amspacher, PhD, __ -AUG-2023

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 8/16/2023 02:45:20PM
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Valerie Amspacher

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

Chapter VI (Biopharmaceutics) of the NDA IQA Guide

NDA Number	NDA-021164-ORIG-1-RESUB-71 (Seq#0005 submitted on 12/23/2022)
Assessment Cycle Number	1
Drug Product Name/ Strength	Gepirone HCl Extended-Release Tablets/ 20 mg, 40 mg, 60 mg, 80 mg (EXXUA™)
Route of Administration	Oral
Applicant Name	Fabre-Kramer Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Psychiatry/CDER/ON/DP
Proposed Indication	Treatment of major depressive disorder in adults

Assessment Recommendation: **Adequate**

Assessment Summary:

Gepirone (Org 33062) Hydrochloride Extended Release (gepirone HCl ER) tablet is a new molecular entity for the treatment of major depressive disorder (MDD). It is a member of the azapirone class and an analog of buspirone. Gepirone HCl ER is to be supplied as 20 mg, 40 mg, 60 mg, and 80 mg tablets. The recommended initial treatment is 20 mg daily, to be increased to 40 mg daily (b) (4). The maximum recommended dose is 80 mg daily.

The original NDA for gepirone HCl ER tablet was submitted on September 30, 1999 and since then resulted in many action letters, General Advice letters from FDA and meetings. Per the Applicant, this NDA Amendment constitutes Fabre-Kramer's complete response to the Division's Appeal Granted letter (March 16, 2016), as well as includes information intended to support the marketing approval of gepirone ER tablets, based on the agreements reached between Fabre-Kramer and the Division at the Type B pre-NDA meeting held on January 31, 2017 and a subsequent pre-NDA Type B meeting held on March 17, 2020.

A brief history of the submissions is summarized in the link below:
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The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) at the time reviewed the clinical pharmacology related submissions in multiple review cycles that included review of bioavailability and bioequivalence studies, and development of dissolution method and specifications. Some reviews that are relevant to the current submission and Biopharmaceutics review are listed below:

1. Memorandom to file: Summary of all the previous reviews by Dr. Di Zhou on 01/11/2016
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af803c9680
2. Clinical pharmacology review of NDA 21164 by Dr. Ronald Kavanagh on October 1, 2007
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80192a28

This review is focused on evaluation and acceptability of the proposed dissolution acceptance criteria, extended-release designation claim, in vitro alcohol-induced dose-dumping potential, formulation bridging, and biowaiver request for gepirone HCl ER tablet, with key findings summarized below.

In Vitro Drug Release Method and Acceptance Criteria: Adequate

The in vitro drug release method for gepirone HCl ER tablets proposed in the original submission was found to be acceptable for Quality Control (QC) purposes per the OCPB reviews mentioned above. However, the Applicant's proposed drug release acceptance criteria were not acceptable and revised acceptance criteria were recommended by the Agency. However, in the current submission, (b) (4) acceptance ranges were proposed. In response to an Information Request (IR), the Applicant tightened the acceptance criteria.

The table below describes the accepted dissolution method and acceptance criteria for the in vitro drug release of all strengths of the proposed drug product.

Strengths	Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL	Acceptance criteria
For all strengths	II (Paddle)	50	0.01 N HCL / 37°C ± 0.5°C	900	1 hour (b) (4) 5 hours (b) (4) 12 hours (b) (4) 20 hours NLT (b) (4)

In Vitro Alcohol-Induced Dose-Dumping: Adequate

The in vitro alcohol-induced dose dumping potential was investigated in 0.01N HCl and 0.1 N HCl in the presence of various concentrations of alcohol (0%, 5%, 10%, 20%, and 40%). Using the current dissolution method, the lowest 20 mg strength, and the highest 80 mg strength gepirone ER tablets were tested from a time point range of 0.25 to 20 hours. No dose dumping was observed for both strengths up to 20 hours in the presence of alcohol concentrations up to 40% (v/v), instead, the dissolution rate of 20 mg and 80 mg gepirone tablets tended to decrease slightly with increasing alcohol concentration in both 0.01N HCl and 0.1N HCl.

Extended Release Claim: Adequate from Biopharmaceutics perspective

The proposed ER drug product was shown to have comparable gepirone bioavailability (BA) between the three ER formulations that are identical to the To-Be-Marketed (TBM) formulation of gepirone and the 10 mg IR capsule dosed twice a day (every 12 hours). Pharmacokinetic data from the above study in conjunction with *in vitro* dissolution data at release and on stability rule out the occurrence of dose-dumping. The data are deemed adequate from Biopharmaceutics perspective to support the extended-release claim for the proposed drug product per the 21 CFR 320.25(f).

Bridging of Clinical and Commercial products: Adequate

The Applicant submitted data from two pivotal bioequivalence (BE) studies in the current submission. BE study FK-GBE-012 demonstrated bioequivalence between the Phase 3 clinical trial (P3CT) gepirone ER 20 mg manufactured at (b) (4) and the TBM gepirone ER 20 mg tablet manufactured at the Mission Pharmacal Company in healthy male subjects under fasting conditions. The data provided by the Applicant are deemed acceptable by Office of Clinical

Pharmacology (OCP). In addition, the drug release profiles of the TBM strengths 20 mg (BE batch), 40 mg, 60 mg, and 80 mg were similar to the clinical BE batch based on the similarity factor (f2). The data provided for bridging between the commercial and clinical BE batches are acceptable.

Biowaiver Request: Adequate

The Applicant's request to waive the in vivo BA/BE studies for the proposed TBM 40 mg, and 60 mg strengths are granted because 1) the submitted pivotal BE studies for the 20 mg and 80 mg strengths are deemed acceptable by the OCP, and dose proportionality within 20 to 80 mg dose range has been established, and (2) the in vitro drug release profile of 40 mg and 60 mg strengths were found to be similar to the bio-strengths (20 mg and 80 mg) as supported by the similarity factor (f2) in both multimedia and QC dissolution medium.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 21164 for the proposed EXXUA™ (gepirone HCl) Extended-Release tablets is recommended for approval.

BIOPHARMACEUTICS ASSESSMENT

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Sequence 0005 (Resubmission, CR response)	12/23/2022
Sequence 0009 (IR response)	02/14/2023 \\CDSESUB1\EVSPROD\nda021164\0009\m1\us\111-information-amendment\multi-module-amend-resprfi20230124and20230127.pdf
Sequence 0016 (IR response)	04/19/2023 \\CDSESUB1\EVSPROD\nda021164\0016\m1\us\111-information-amendment\multi-module-amend-inforequest20230403.pdf

Highlight Key Issues from Last Review Cycle: None

Concise Description of Outstanding Issues: None

DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***Adequate***

The in vitro drug release method for gepirone HCl ER tablets was found to be acceptable per the OCPB reviews mentioned below.

https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af803c9680
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80192a28

The Applicant noted that analytical procedures for the finished product remain the same as specified in the NDA 21164 Amendment submission dated May 1, 2007.

The Sponsor's originally proposed dissolution acceptance criteria were:

1 hour 15% - 25%
5 hours 40% - 85%
12 hours 65% - 86%
20 hours > (b) (4) %

Per the reviews above, dissolution acceptance criteria were not acceptable, and the Applicant was requested to adopt the following acceptance criteria:

1 hour (b) (4)
5 hours
12 hours
20 hours NLT (b) (4) %

However, in the current submission, wider acceptance ranges were proposed. The Applicant noted that dissolution timepoint ranges were adjusted to reflect slight differences in assay results from different sites as proposed below:

1 hour (b) (4)
5 hours
12 hours
20 Hours NLT (b) (4) %

The above acceptance criteria were permissive and not acceptable. The applicant was requested to revise the acceptance criteria per the current Agency's guideline based on mean target value (b) (4) for the last specification time-point (See IR2.2 in Appendix 1). In the response the Applicant tightened and proposed below acceptance criteria. Biobatch 98-013T, gepirone HCl ER tablet 20 mg, manufactured by (b) (4) conforms to this acceptance criteria at the time of release.

1 hour (b) (4)
5 hours
12 hours
20 hours NLT (b) (4) %

In an email dated August 29, 2023, the applicant stated that there was a typo when they agreed to the above dissolution acceptance criterion at 20 hours. They stated that the acceptance criterion at 20 hours should be NLT (b) (4) %. The proposed acceptance criterion is acceptable.

In-Vitro Alcohol Dose Dumping

Assessment: *Adequate*

In response to an IR (see IR1.6 in Appendix 1), the Applicant referred to the study report DQLN010-1 for alcohol dose dumping that was provided in the current submission in the link below:
\\CDSESUB1\EVSPROD\nda021164\0005\m4\42-stud-rep\422-pk\4227-other-pk-stud\dqln010-1\dqln010-1-pre-clinical-study-report.pdf

The in vitro alcohol-induced dose dumping potential was investigated using media with ethanol concentrations at 0%, 5%, 10%, 20% and 40%. Gepirone ER tablets are extended-release formulations designed to meter each dose over 20 hours. Using the current dissolution method, tablets were tested in 0.01N HCl, and additionally 0.1 N HCl, using a time point range of 0.25 to 20 hours. Dissolution tests of twelve tablets were performed using the lowest strength, 20 mg gepirone tablets, lot 09Xl8 and the highest strength, 80 mg gepirone tablets, lot l0Xl8. The results for the dissolution testing are shown in the figures below.

Figure 1 – Plot Comparing Mean 20 mg Gepirone Tablet Results 0.01N HCl

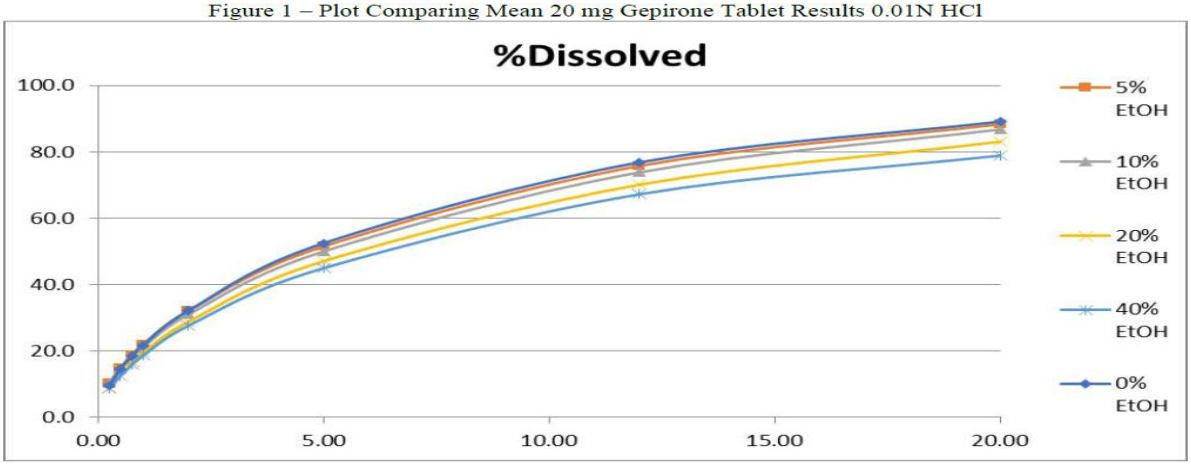


Figure 2 – Plot Comparing Mean 20 mg Gepirone Tablet Results 0.1N HCl

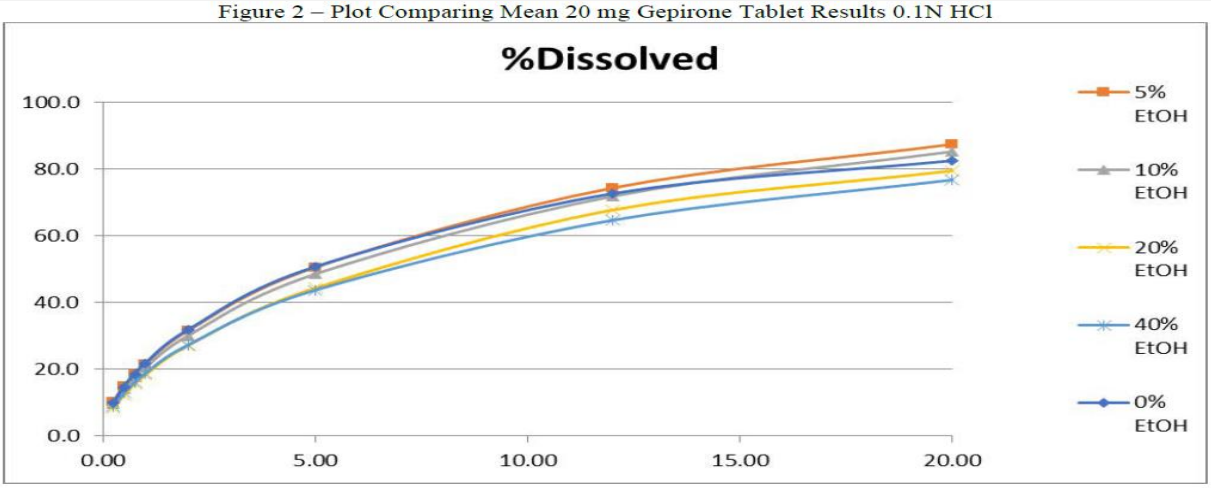


Figure 3 – Plot Comparing Mean 80 mg Gepirone Tablet Results 0.01N HCl

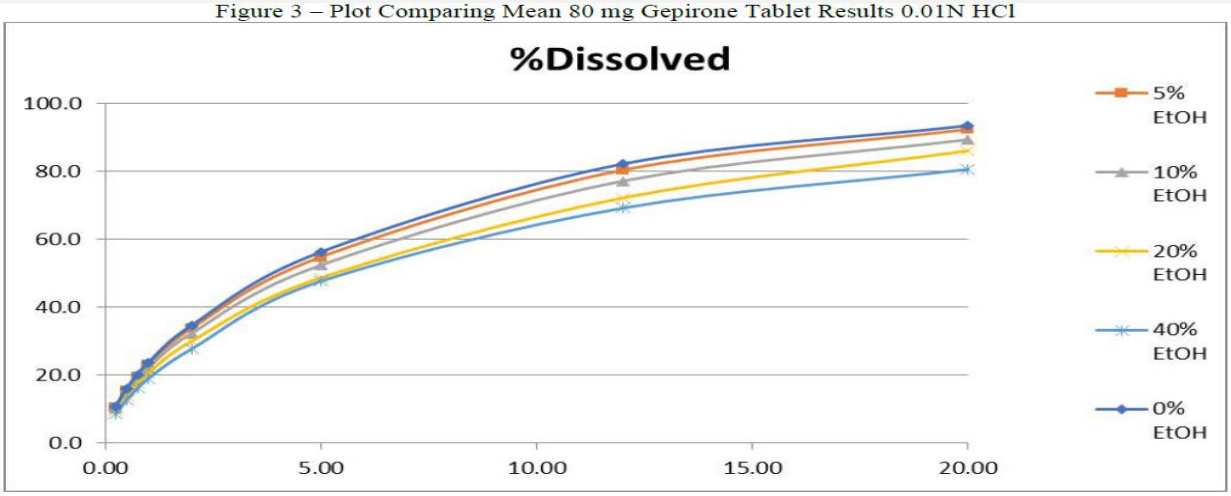
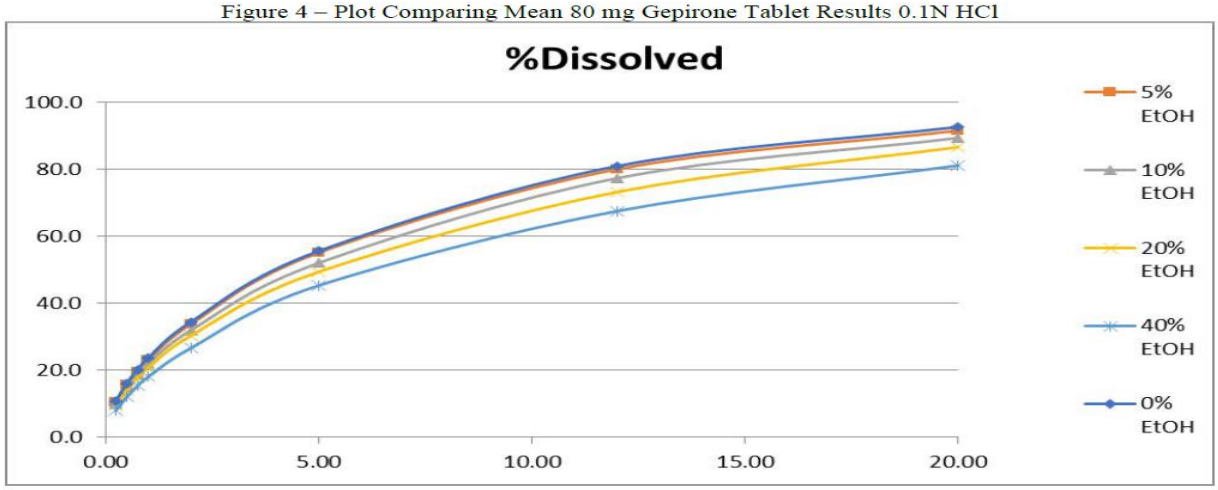


Figure 4 – Plot Comparing Mean 80 mg Gepirone Tablet Results 0.1N HCl



The dissolution rate of 20 mg and 80 mg gepirone ER tablets tended to decrease slightly with increasing ethanol concentration in both 0.01N HCl and 0.1N HCl. Similarity factor (f2) showed similar release profiles for 20 mg and 80 mg tablets in presence of alcohol, but there was a trend towards decreasing dissolution as ethanol concentration increased. These results suggest the risk of alcohol-induced dose dumping during dissolution of gepirone ER tablets over the full range of tablet strengths is minimal. (b) (4)

EXTENDED-RELEASE CLAIM

Assessment: *Adequate from Biopharmaceutics perspective*

In response to an IR (see IR1.5 in Appendix 1), the Applicant referred to Study CN105-026 to support the extended-release claim of the proposed drug product, per criteria in 21 CFR 320.25(f). Study CN105-026 is a relative bioavailability study of three gepirone ER formulations and the 10 mg IR capsule dosed twice a day (every 12 hours).

Patients selected to participate in this study were healthy adult male volunteers, 19 to 36 years of age. In this study, all the subjects received:
• Treatment # 1 2 x 10 mg tablets of ER Org 33062 (ER-1)
• Treatment # 2 2 x 10 mg tablets of ER Org 33062 (ER-2)
• Treatment # 3 1 x 25 mg tablet of ER Org 33062 (ER-3)
• Treatment # 4 2 x 5 mg Org 33062 IR capsules every 12 hours

The ER-1 and ER-2 formulations used in the study are virtually identical to the TBM formulation of gepirone (i.e., Mission formulation).

The mean pharmacokinetic results from the 12 subjects who completed the trial are summarized in the table below.

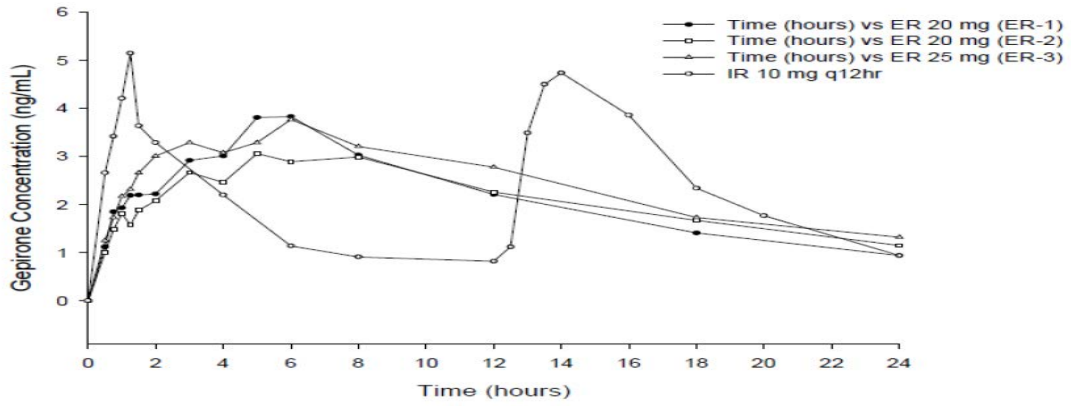
Mean (SD) Pharmacokinetic Parameters for Gepirone and 1-PP: Study CN105-026 (N = 12)

	Treatment Group [1]			
Gepirone				
C_{max} (ng/mL) [3]	4.3 (2.8)	3.7 (2.2)	3.6 (1.6)	12.2 (6.3)[4]
T_{max} (hours)	5.1 (1.6)	5.6 (2.5)	4.8 (1.9)	1.3 (0.9)[2]
AUC_{30} (ng•hr/mL) [3]	55.3 (28.2)	55.0 (33.7)	51.8 (27.3)	54.9 (25.6)
1-PP				
	ER-1	**ER-2**	**ER-3**	**IR Capsules**
C_{max} (ng/mL) [3]	4.2 (1.6)	3.7 (1.6)	3.6 (1.8)	12.5 (4.3)[5]
T_{max} (hours)	5.7 (1.6)	5.1 (2.0)	5.6 (2.5)	1.7 (0.8)[2]
AUC_{30} (ng•hr/mL) [3]	74.0 (40.8)	68.2 (40.2)	67.6 (41.6)	92.8 (56.8)[5]

[1] 1: Org 33062 ER 20 mg x 1 (ER-1)
2: Org 33062 ER 20 mg x 1 (ER-2)
3: Org 33062 ER 25 mg x 1 (ER-3)
4: Org 33062 IR 10 mg q12h x 2
[2] C_{max} and T_{max} after the 1st dose of Org 33062
[3] dose-normalized to 20 mg
[4] Trt 4 > Trt 1, 2, and 3, $p < 0.0083$, unequal variance t-test
[5] Trt 4 > Trt 1, 2, and 3, $p < 0.05$, Tukey's test

The mean Tmax for gepirone ranged between 4.8-5.6 hours after dosing with the ER formulations compared to 1.3 hours after the first dose of the IR formulation. There were no significant differences in mean AUC between the ER and IR formulations at the same dose. The mean Cmax after administration of the IR capsules was significantly higher than after administration of the ER formulations. The average plasma concentrations for all three formulations indicates that the ER formulation achieves the desired characteristics of reducing the peak-trough fluctuation (Figure below).

Average Gepirone Plasma Concentration Following Administration of Org 33062 ER Tablet and Org 33062 IR Capsules: Study CN105-026



Per the summary in 2016 OCP review, bioavailability of the two formulations was comparable (ER q.d vs IR b.i.d). Pharmacokinetic data from the above study in conjunction with *in vitro* dissolution data at release and on stability, rule out the occurrence of dose-dumping, with consistent delivery of gepirone with coefficients of variations for Cmax and AUC of approximately 25% on Day 1 and at steady-state. The data are deemed adequate from Biopharmaceutics perspective to support the extended-release claim for the proposed drug product per the 21 CFR 320.25(f).

BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The Applicant noted that the qualitative and quantitative composition, shape and size of tablets remain the same, as well as the debossing described in the 2007 Amendment. Per the 2007 OCP review and as summarized in 2016 OCP review, comparative dissolution studies in multiple media between the previous Organon biconvex and modified flat tablets and the new Fabre-Kramer modified flat tablets were acceptable.

In the current submission, the Applicant has proposed Mission Pharmacal Company as the new commercial drug product manufacturer and site for regulatory release of the finished product. In 2007 submission, manufacturer (b) (4) was mentioned as the drug product manufacturer and site for regulatory release of the finished product. (b) (4) is the clinical trial formulation manufacturer for gepirone ER tablet 20 mg that was used in various BE studies. In response to an IR (see IR2.4 in Appendix), the Applicant confirmed that the pivotal clinical trial batches were manufactured at (b) (4) However, the facility has undergone a change in name only, therefore, (b) (4) will henceforth be identified as (b) (4) The Applicant further noted that (b) (4) are used interchangeably in the submission. The previous gepirone ER tablet contract manufacturing facility had (b) (4) during the relevant time period. (b) (4) was the original owner of the facility. (b) (4) .

The Applicant conducted two new pivotal BE studies and submitted the data in the current submission. BE study FK-GBE-012 was conducted to demonstrate bioequivalence between the Phase 3 clinical trial (P3CT) gepirone ER 20 mg manufactured at (b) (4) and the TBM gepirone ER 20 mg tablet manufactured at the Mission Pharmacal Company (FMI: Final Market Image) in healthy male subjects under fasting conditions. Moreover, pivotal BE study FK-GBE-14 was conducted to demonstrate bioequivalence between the P3CT gepirone ER 20 mg x four and FMI EXXUA 80 mg x one in healthy male subjects under fasting conditions. The compositions of the batches used in these BE studies are provided below.

Table 3.2.P.2-3 Composition Information for Study Drugs, Fabre-Kramer Clinical Studies FK-GBE-011, FK-GBE-012 or FK-GBE-014

Manufacturer	(b) (4)	Mission	Mission
Batch No.	**98-013T**	**8L015**	**8L036**
Oral Dosage Form	tablet	tablet	tablet
Gepirone HCl API	20.0 mg (b) (4)	20.0 mg (b) (4)	80.0 mg (b) (4)
Hypromellose, (b) (4)	(b) (4)		
Microcrystalline Cellulose (b) (4) (b) (4)			
Colloidal silicon dioxide			
Magnesium stearate			
Red (b) (4) oxide			
Yellow (b) (4) oxide			
Total mass	**375.0 mg**	**375.0 mg**	**410.0 mg**

The above BE studies are under the purview of OCP. In an email on 04/03/2023 and 04/20/2023, OCP reviewer, Dr. Kofi Kumi indicated that 20 mg TBM formulation is bioequivalent to 20 mg

clinical trial material (Study FK-GBE-012) and 80 mg TBM formulation is BE to 4 x 20 mg clinical trial material (Study FK-GBE-14). OCP review is currently pending.

The Applicant has provided comparative dissolution data for the batches used in above BE studies. Per the below table, the 20 mg clinical lot used in two Pivotal BE studies is 98-013T. This batch was manufactured in April 1998 per the table below whereas the TBM 20 mg (batch 8L015) was manufactured in dec 2018.

Table 3.2.P.2-1 Batch Information for Fabre-Kramer Clinical Studies (post-2007)

Clinical Protocol	Clinical Phase	Gepirone Dosage Forms	Clinical Batch #	Mfg Date	Drug Substance Batch #	Batch Size # of units	Formulation
FK-GBE-010 (TQT Study)	1	50 mg capsule, IR matching Placebo capsule	44X18 43X18	01Nov2018 30Oct2018	A170002 NA	(b) (4)	Table 3.2.P.2-2
FK-GBE-011[1]	1	20 mg FMI Formulation[4,6] 20 mg P3CT Formulation[7] 80 mg FMI Formulation[5,6]	8L015 98-013T 8L036	05Dec2018 Apr1998 05Dec2018	[4] 0198001 [5]		Table 3.2.P.2-3
FK-GBE-012[2]	1	20 mg FMI Formulation[4,6] 20 mg P3CT Formulation[7]	8L015 98-013T	05Dec2018 Apr1998	[4] 0198001		Table 3.2.P.2-3
FK-GBE-014[3]	1	20 mg P3CT Formulation[7] 80 mg ER tablet[5,6]	98-013T 8L036	Apr1998 05Dec2018	0198001 [5]		Table 3.2.P.2-3

1 BE study: comparison, 20 mg FMI Gepirone ER Mission and 20 mg P3CT Gepirone ER (b) (4) batches: compared historical data from previous BE study that included this (b) (4) batch. PK study: Mission 20 mg, fasted. PK study: Mission 80 mg, fasted. PK study: dose proportionality, 20 mg Mission relative to 80 mg Mission batches.

2 BE study: comparison, 20 mg FMI Gepirone ER Mission and 4 x 20 mg, P3CT Gepirone ER (b) (4) batch.

3 BE study: comparison, 80 mg FMI Gepirone ER Mission and 4 x 20 mg, P3CT Gepirone ER (b) (4) batch. PK profiles were also obtained and compared.

4 The 20 mg Gepirone HCl ER tablets manufactured in 2018 by Mission are pink, modified rectangular shaped, debossed with "FK" on one side and "1" on the other side. Batch 8L015 contained (b) (4)% DS Batch A170002 and (b) (4)% A170004.

5 The 80 mg Gepirone HCl ER tablets manufactured in 2018 by Mission are red-brown, modified rectangular shaped, debossed with "FK" on one side and "17" on the other side. Batch 8L036 contained (b) (4)% DS Batch A170003 and (b) (4)% A170005.

6 Mission ER Formulation = Final Market Image [FMI] Formulation

7 (b) (4) 20 mg ER Formulation = Phase 3 Clinical Trial [P3CT] Formulation; [DS Batch 0198001 = (b) (4) Batch 980272]

Comparative dissolution data (clinical lot tested on Sept 2018) for these two batches are shown below. Based on the similarity factor calculated by this reviewer taking 4 data points available for clinical lot (f2=79), the dissolution profiles of the clinical lot and TBM lots used in the two BE studies are similar.

Mfr>>	Mission; 20 mg Gepirone Tablet, lot 8L015			(b) (4) 20 mg Gepirone Tablet, lot 98-013T		
Time (hr)	Range	Mean	%RSD	Range	Mean	%RSD
0.25	(b) (4)	10.6	2.1	(b) (4)	NT	NT
0.5		15.4	2.0		NT	NT
0.75		19.4	2.1		NT	NT
1		22.9	2.1		20.8	1.36
2		33.6	2.0		NT	NT
5		54.7	2.2		51.8	1.8
8		68.4	1.9		NT	NT
12		80.7	1.5		78.2	1.3
15		86.9	1.3		NT	NT
20		93.9	1.3		92.1	0.9

NT-Not tested. Test date, (b) (4) lot, 10Sep2018.

The in vitro drug release profiles of the clinical lot 98-013T submitted currently (2018 testing) and submitted before 2004 (per the data found in 2004 OCP review) are similar based on the similarity factor (f2) indicating adequacy of clinical trial material from Biopharmaceutics perspective as inquired by OCP in an email on 03/30/2023.

Table E. Drug Release Profiles of the Validation Batches vs. the Reference Product.

		% Dissolved				
Control #	Strength, mg	1st Hr	5th Hr	12th Hr	20th Hr	Recovery
98 –013T	20	19	49	77	93	102
0300422	40	21	51	79	94	101
0300423	40	21	51	78	93	100
0300424	60	22	53	81	95	101
0300425	60	22	53	81	95	102
0300468	80	22	53	81	96	101
0300469	80	21	52	81	97	102

The in vitro drug release data as shown below for 40 mg, 60 mg and 80 mg strength TBM lots showed that the similarity factor (f2) was greater than 50 when compared to the 20 mg TBM lot indicating equivalency in release profiles amongst all the strengths.

Table 3.2.P.5.4-7 Test Results for Tablets in the Proposed Fabre-Kramer Market Image. Full Scale, (b) (4) Tablet Batches

Test	Lot 8L015 (20 mg)	Lot 8K038 (40 mg)	Lot 8K052 (60 mg)	Lot 8L036 (80 mg)
Description	Pass	Pass	Pass	Pass
Identification				
Gepirone (HPLC)	Pass	Pass	Pass	Pass
Gepirone (UV)	Pass	Pass	Pass	Pass
(b) (4) oxide	Pass	Pass	Pass	Pass
Average tablet weight	373 mg/Tablet	390 mg/Tablet	389 mg/Tablet	417 mg/Tablet
Uniformity of mass	Pass	Pass	Pass	Pass
Gepirone HCl Assay	98.1%	101.0%	101.0%	99.7%
Content Uniformity	Pass	Pass	Pass	Pass
Drug release (Dissolution)	1st: 22% 5th: 53% 12th: 79% 20th: 92%	1st: 23% 5th: 55% 12th: 81% 20th: 95%	1st: 23% 5th: 57% 12th: 85% 20th: 98%	1st: 24% 5th: 58% 12th: 84% 20th: 99%
(b) (4) • Identified Related Substances (b) (4) (b) (4) • Unspecified Degradation Products • Total degradation products	(b) (4)			

Based on the above study results, bridging between the commercial and clinical batches are acceptable.

BIOWAIVER REQUEST

Assessment: *Adequate*

In response to the IRs (see IR1.4 and IR2.3 in Appendix 1) in the current review cycle, the Applicant submitted a formal biowaiver request to waive the in vivo bioavailability studies for the proposed TBM 40 mg, and 60 mg strengths.

In FDA Correspondence dated March 17, 2020 to the Applicant, the Agency indicated that bioequivalence data for the 20 mg and 80 mg dose strengths would be required to support approval, and disagreed with the Applicant's request to waive the BE study requirement for the highest strength 80 mg. According to the meeting minutes dated March 1, 2017 for the Type B meeting held on January 30, 2017, the Applicant needed to demonstrate PK bridging between the to-be-marketed product used in the past successful efficacy studies. Given that the different strengths of the product are not compositionally proportional, they should establish BE for both the lowest planned strength (20 mg) and the highest planned strength (80 mg). Subsequently, the Applicant conducted two pivotal BE studies, namely FK-GBE-012 and FK-GBE-014 and submitted results of these studies in the current submission (located: 2022 NDA 021164 - eCTD sequences > 0005 > m5 > 5.3.1.2).

The results of pivotal BE study FK-GBE-012 demonstrates bioequivalence between the Phase 3 clinical trial (P3CT) gepirone ER 20 mg and the TBM tablet gepirone ER 20 mg in healthy male subjects under fasting conditions. Moreover, the results of the pivotal BE study FK-GBE-14 demonstrates bioequivalence between the P3CT gepirone ER 20 mg x four and the TBM 80 mg x one in healthy male subjects under fasting conditions. The Applicant also noted that results of Study FK-GBE-011 have demonstrated rough dose proportionality of the PK parameters of gepirone across the 20-80 mg dose range supporting linear pharmacokinetics across the clinical dose range. The submitted pivotal BE studies for the 20 mg and 80 mg strengths are deemed acceptable by the OCP as confirmed in the email dated 4/3/2023 and 4/20/2023. OCP also confirmed that the OCP reviews from previous cycle indicate that the PK is linear from 20 mg to 80 mg. Given the dose proportionality within 20 to 80 mg dose range as well as bioequivalence at the 20 mg and 80 mg dose levels, bioequivalence of the 40 mg and 60 mg dosage form of the TBM product is implied.

Comparative dissolution data for the clinical lot and all strengths of TBM drug product in QC medium show that the dissolution profiles are similar based on the similarity factor (f2). Please see the details in Bridging of Formulation section.

In response to the IRs, the Applicant also submitted comparative dissolution data in multimedia (0.01 N HCl, pH 4.5 buffer, pH 6.8 buffer, and DWI (USP Water for Injection). These dissolution profiles demonstrate similarity based on f2 criteria across the 20-80 mg dose range for the TBM products as verified by this reviewer.

In conclusion, the in vitro drug release profiles of 40 mg and 60 mg strengths were found to be similar to the bio-strengths (20 mg and 80 mg) as supported by the similarity factor (f2) in both multimedia and QC dissolution medium. Hence, the biowaiver request for the 40 mg and 60 mg strengths is granted based on the acceptable BA/BE study and dissolution data.

RECOMMENDATION:
From the Biopharmaceutics perspective, NDA 21164 for the proposed EXXUA™ (gepirone HCl) Extended-Release tablets is Adequate.

Primary Biopharmaceutics Assessor's Name: Dr. Kalpana Paudel, Ph.D.
Secondary Assessor Name: Dr. Okpo Eradiri, Ph.D.

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Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 8/29/2023 09:09:06PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 8/30/2023 08:24:29AM
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Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 8/31/2023 09:31:22AM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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/s/

VALERIE R AMSPACHER
08/31/2023 09:38:16 AM

NDA 21-164

Gepirone HCl Extended Release Tablet

Fabre-Kramer Pharmaceuticals, Inc.

Sherita D. McLamore, Ph.D.

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-164

2. REVIEW # 6

3. REVIEW DATE: August 15, 2007

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	09/18/99
Original Submission Re-submitted	05/18/01
Amendment	02/15/02
Amendment	06/23/04
Amendment	05/1/07

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10/9/07

7. NAME & ADDRESS OF APPLICANT:

Name: Fabre-Kramer Pharmaceuticals, Inc.

Address: 5847 San Felipe, Suite 2000
Houston, TX 77057

Representative: Damaris DeGraft-Johnson

Telephone: 610.558.4454

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Travivo
b) Non-Proprietary Name (USAN): Gepirone Hydrochloride
c) Code Name/# (ONDC only): ORG 33062
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 20, 40, 60 and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

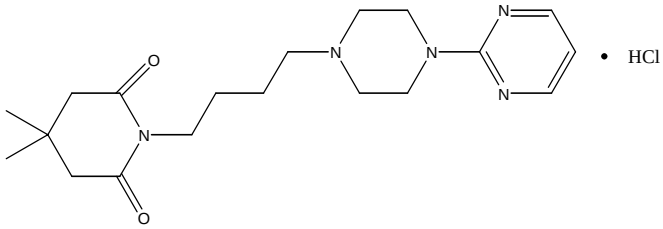
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 2,6-piperidinedione-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl] monohydrochloride
Molecular Formula: $C_{19}H_{29}N_5O_2$. HCl
Molecular Weight: 395.93



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF (b) (4)	Type II	(b) (4)		3	Adequate	02-5-02	N/A
DMF (b) (4)	Type III			4	N/A		N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	23,952	Gepirone Immediate Release Tablets, depression
IND	33,626	Gepirone Sustained Release Formulation (extended release tablets) for depression
IND	(b) (4)	Gepirone HCl (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	10/30/07	Office of Compliance
Pharm/Tox	Pending	Pending	Linda Fossom, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
DMETS	Pending	Pending	
EA	Categorical Exclusion	8/1/07	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

Chemistry Assessment Section

The Chemistry Review for NDA 21-164

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-164 is approvable from a Chemistry, Manufacturing and Control perspective. The applicant responded to the September 27, 2007 IR letter. Additionally, all of the sites submitted to the Office of Compliance were found acceptable and an overall recommendation of acceptable was issued for this application on October 30, 2007 At this time, we are requesting that the applicant provide stability data on the commercial drug product in each of the proposed packaging configuration as there is no data currently available for the to be marketed product. We are also requesting that the applicant revise the proposed acceptance criterion for individual unspecified impurity to NMT (b)(4)% as the currently proposed acceptance criteria of (b)(4)% is not in accordance with ICH Q3B guideline. The following comments should be included in the action letter.

1. The provided stability data for the original biconvex tablets and the Organon modified flat tablets is not sufficient to support your request for 36 month expiration date for the drug product. Please provide long-term and accelerated stability data for the commercial to-be-marketed drug product in each of the proposed packaging configurations.

2. Revise your acceptance criterion for individual unspecified impurity to NMT (b)(4)% in accordance with ICH Q3B guideline. Any individual impurities at levels higher than identification threshold of (b)(4)% should be specified by name, relative retention time or some other suitable identifier.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Gepirone Hydrochloride is a member of the azapirone class of compounds and is indicated for the treatment of patients with major depressive disorder. The drug product, gepirone hydrochloride, is a new molecular entity and accordingly the applicant claims exclusivity for the drug product. Gepirone was originally developed by Mead Johnson and Bristol Myers

Company then later by Organon. The product was licensed to the applicant, Fabre-Kramer Pharmaceuticals in 1993.

The drug substance is described as a white to off-white crystalline powder with a melting point of 180°C. The molecular formula for the drug substance is $C_{19}H_{29}N_5O_2 \cdot HCl$ and the molecular weight is 395.93. The drug substance exists in two different polymorphic forms. The applicant indicates that (b) (4) used in the manufacture of the drug product and provided identification and testing for the presence of polymorphic (b) (4) and the absence of polymorphic (b) (4) The synthesis and characterization of the drug substance is described in detail in (b) (4) Type II DMF (b) (4) The drug substance manufacturer remains unchanged from the previous submission. The applicant provides the corresponding letter of authorization for this DMF and indicates that the DMF was updated in April of 2006 by the holder. The DMF was previously reviewed and found adequate to support this application. The only changes other than format changes to the new CTD format in the April 2006 amendment were a stability update and an update to the batch size to better reflect the current production.

Gepirone Hydrochloride Extended Release Tablets are available in 20, 40, 60 and 80 mg strengths. The tablets are a modified-rectangular shaped debossed tablets each with similar weights and different colors. The 20 mg tablets are pink with "FK" on one side and "1" on the other. The 40 mg tablets are off-white with "FK" on one side and "7" on the other. The 60 mg tablets are yellow with "FK" on one side and "11" on the other. The 80 mg tablets are red-brown with "FK" on one side and "17" on the other. In the original submission, the shape of the tablets was a biconvex. In the December 2003 submission, the tablet shape changed from biconvex to flat. In the current submission, the tablet shape remains unchanged from the previous submission. There have been no other changes to the tablet composition, shape or size since the December 2003 submission. The applicant has included comparative dissolution data with f_1 and f_2 comparisons for all strengths of the drug product. The comparisons were of the Fabre-Kramer product and the Organon products (flat and biconvex tablets). The tablets will be packaged in 30, 100 and 500 count (b) (4) HDPE bottles with a child resistant (b) (4) closures. Additionally, (b) (4) as described in the December 2003 submission.

The qualitative and quantitative composition, method of manufacture and the specifications for the drug product remain unchanged. The drug product is manufactured (b) (4) The dissolution specification for the drug product is 1st hour: 15-25%; 5th hour: 40-(b) (4)%; 12th hour 65-86% and 20th hour: NLT 86%. The dissolution specification and all other specifications provided by the applicant are acceptable.

The applicant has requested a 36 month expiration dating for all potencies of the drug product. The applicant provides (b) (4) The stability data is for the Organon product which has the same shape as the to-be marketed product but with a different debossing. The applicant does not provide any stability data on the actual commercial drug product but commits to placing batches with commercial debossing on stability in bottles (b) (4). The applicant has included 36 months of long term and 6 months accelerated stability data for the original biconvex tablets manufactured by Organon. All data provided for the modified flat and biconvex tablets were within specification; however, the applicant has not provided adequate data to support the requested 36 month expiry as there has been no data submitted for the commercial product and limited data for modified flat tablets manufactured by Organon.

Originally, the proposed proprietary name for the drug product was Ariza (Gepirone HCl Extended-Release Tablets) 20 mg, 40 mg, 60 mg and 80 mg. The Office of Post –Marketing Drug Risk Assessment (OPDRA) concluded that Ariza was not an acceptable name for the drug product. On February 9, 2004, the applicant proposed the use of the name VARIZA™ and Variza™ as a trademark name for the drug product and in this submission, the applicant proposes to use the trade name Travivo™.

B. Description of How the Drug Product is Intended to be Used

Gepirone Hydrochloride Extended Release Tablets are being developed for the treatment of depression. The recommended starting dose is 20 mg per day. The applicant indicates that the dose should be increased to 40 mg per day (b) (4) the dose may be increased to a maximum dose of 80 mg per day (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-164 is **Approvable** from the chemistry, manufacturing and controls (CMC) standpoint. During the September 14, 2007 teleconference, it was confirmed that the source of the problems associated with biconvex tablets was (b) (4). As a result, the original applicant, Organon, changed (b) (4) from the biconvex to the modified flat. The applicant, Fabre-Krammer, was asked to provide data to show that the aforementioned (b) (4) problems have been eliminated. The applicant responded to this request and included (b) (4) data. To date, (b) (4) There is no data on this formulation available on the product packaged in bottles and there is no data on the commercial drug product. Originally, the applicant had been advised that the data on the modified flat Organon product would be considered as primary stability data before the company made yet another (b) (4) change. The provided data is not sufficient to grant requested 36 month expiration date considering the (b) (4) and

(b) (4) problems associated with product. Moreover, the clinical division will be recommending a NA action for this application. Considering all these factors we are requesting that the applicant provides additional stability data on the to-be marketed drug product in each of the commercial packaging configurations upon resubmission. Additionally, the acceptance criteria proposed for the unspecified impurity is (b) (4)%. The maximum daily intake for the drug product is 80 mg, accordingly, the identification threshold should be (b) (4)%. We are requesting that the applicant revise the acceptance criteria for the individual unspecified impurity to NMT (b) (4)% in accordance with ICH Q3B guideline.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
SMcLamore
RSood

C. CC Block
Orig. NDA 21-164
HFD-120/SMcLamore
HFD-120/TOliver

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/s/

Sherita McLamore
10/30/2007 04:12:41 PM
CHEMIST

Ramesh Sood
10/31/2007 08:42:20 AM
CHEMIST

NDA 21-164

Gepirone HCl Extended Release Tablet

Fabre-Kramer Pharmaceuticals, Inc.

Sherita D. McLamore, Ph.D.

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-164

2. REVIEW # 5

3. REVIEW DATE: August 15, 2007

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	09/18/99
Original Submission Re-submitted	05/18/01
Amendment	02/15/02
Amendment	06/23/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	05/1/07

7. NAME & ADDRESS OF APPLICANT:

Name: Fabre-Kramer Pharmaceuticals, Inc.

Address: 5847 San Felipe, Suite 2000
Houston, TX 77057

Representative: Edna Gilvary, Ph.D.

Telephone: 713.977.1574

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Travivo
b) Non-Proprietary Name (USAN): Gepirone Hydrochloride
c) Code Name/# (ONDC only): ORG 33062
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 1

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 20, 40, 60 and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

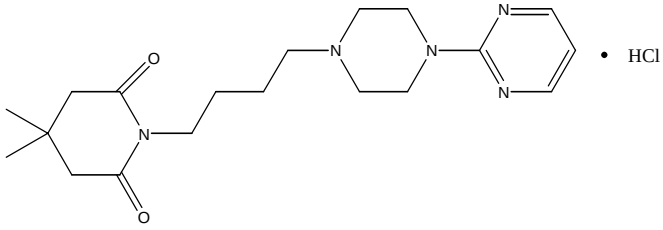
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 2,6-piperidinedione-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl] monohydrochloride
Molecular Formula: $C_{19}H_{29}N_5O_2$. HCl
Molecular Weight: 395.93



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)		3	Adequate	02-5-02	N/A
	Type III			4	N/A		N/A

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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6 – DMF not available
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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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IND	33,626	Gepirone Sustained Release Formulation (extended release tablets) for depression
IND	(b) (4)	Gepirone HCl (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Office of Compliance
Pharm/Tox	Pending	Pending	Linda Fossom, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
DMETS	Pending	Pending	
EA	Categorical Exclusion	8/1/07	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

Chemistry Assessment Section

The Chemistry Review for NDA 21-164

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-164 is approvable from a Chemistry, Manufacturing and Control perspective. The Office of Compliance will need to find all sites acceptable (overall recommendation is still pending).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Gepirone Hydrochloride is a member of the azapirone class of compounds and is indicated for the treatment of patients with major depressive disorder. The drug product, gepirone hydrochloride, is a new molecular entity and accordingly the applicant claims exclusivity for the drug product. Gepirone was originally developed by Mead Johnson and Bristol Myers Company then later by Organon. The product was licensed to the applicant, Fabre-Kramer Pharmaceuticals in 1993.

The drug substance is described as a white to off-white crystalline powder with a melting point of 180°C. The molecular formula for the drug substance is $C_{19}H_{29}N_5O_2 \cdot HCl$ and the molecular weight is 395.93. The drug substance exists in two different polymorphic forms. The applicant indicates that (b) (4) used in the manufacture of the drug product and provided identification and testing for the presence of polymorphic (b) (4) and the absence of polymorphic (b) (4) The synthesis and characterization of the drug substance is described in detail in (b) (4) Type II DMF (b) (4) The drug substance manufacturer remains unchanged from the previous submission. The applicant provides the corresponding letter of authorization for this DMF and indicates that the DMF was updated in April of 2006 by the holder. The DMF was previously reviewed and found adequate to support this application. The only changes other than format changes to the new CTD format in the April 2006 amendment were a stability update and an update to the batch size to better reflect the current production.

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The qualitative and quantitative composition, method of manufacture and the specifications for the drug product remain unchanged. The drug product is manufactured i (b) (4) The dissolution specification for the drug product is 1st hour: 15-25%; 5th hour: 40- (b) (4)%; 12th hour 65-86% and 20th hour: NLT 86%. The dissolution specification and all other specifications provided by the applicant are acceptable.

The applicant has requested a 36 month expiration dating for all potencies of the drug product. The applicant provides (b) (4) The stability data is for the Organon product which has the same shape as the to-be marketed product but with a different debossing. The applicant does not provide any stability data on the actual commercial drug product but commits to placing batches with commercial debossing on stability in bottles (b) (4). The applicant has included 36 months of long term and 6 months accelerated stability data for the original biconvex tablets manufactured by Organon. All data provided for the modified flat and biconvex tablets were within specification; however, the applicant has not provided adequate data to support the requested 36 month expiry as there has been no data submitted for the commercial product and limited data for modified flat tablets manufactured by Organon.

Originally, the proposed proprietary name for the drug product was Ariza (Gepirone HCl Extended-Release Tablets) 20 mg, 40 mg, 60 mg and 80 mg. The Office of Post –Marketing Drug Risk Assessment (OPDRA) concluded that Ariza was not an acceptable name for the drug product. On February 9, 2004, the applicant proposed the use of the name VARIZA™

and Variza™ as a trademark name for the drug product and in this submission, the applicant proposes to use the trade name Travivo™.

B. Description of How the Drug Product is Intended to be Used

Gepirone Hydrochloride Extended Release Tablets are being developed for the treatment of depression. The recommended starting dose is 20 mg per day. The applicant indicates that the dose should be increased to 40 mg per day (b) (4) the dose may be increased to a maximum dose of 80 mg per day (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-164 is **Approvable** from the chemistry, manufacturing and controls (CMC) standpoint. The Office of Compliance will need to find all sites acceptable (currently Office of Compliance decision is pending) before the application can be approved. Additionally, during the September 14, 2007 teleconference, it was confirmed that the source of the problems associated with biconvex tablets was (b) (4). As a result, the original applicant, Organon, changed (b) (4) from the biconvex to the modified flat. The applicant, Fabre-Krammer, was asked to provide data to show that the aforementioned (b) (4) problems have been eliminated. At this time, we are waiting for additional data to evaluate if the problems associated with (b) (4) change have been eliminated. The drug product expiration will be assigned based on data that the company has promised to submit. As of now, (b) (4) There is no data on this formulation available on the product packaged in bottles. The applicant has been advised that the data on the modified flat Organon product will be considered as primary data.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore
RSood

C. CC Block

Orig. NDA 21-164
HFD-120/Division File
HFD-120/SMcLamore
HFD-120/TOliver

25 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

Sherita McLamore
9/24/2007 11:48:41 AM
CHEMIST

Ramesh Sood
9/24/2007 01:55:32 PM
CHEMIST

Chemistry Review Data Sheet

NDA 21-164

Variza™ (Gepirone Hydrochloride) Extended Release Tablet

Organon, Inc.

Sherita D. McLamore, Ph.D.
HFD-120

Chemistry Review Data Sheet

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-164

2. REVIEW # 4

3. REVIEW DATE: April 30, 2004

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	5/18/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	2/15/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon, Inc.
Address:	375 Mount Pleasant Avenue West Orange, NJ 07052
Representative:	Edna Gilvary, Ph.D.
Telephone:	973.325.4627

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Variza
b) Non-Proprietary Name (USAN): Gepirone Hydrochloride
c) Code Name/# (ONDC only): ORG 33062

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 20, 40, 60 and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

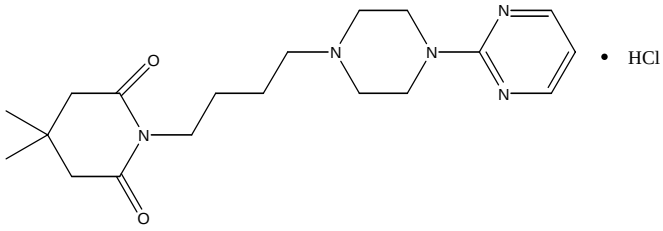
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 3,3-Dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]glutarimide mono-hydrochloride
Molecular Formula: $C_{19}H_{29}N_5O_2$. HCl
Molecular Weight: 395.93



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	1	Adequate	02-5-02	N/A
	Type III			1	Adequate	09-28-00	N/A
	Type III			1	Adequate	09-26-00	N/A
	Type III			1	Adequate	08-25-98	N/A
	Type III			1	Adequate	09-19-00	N/A
	Type III			1	Adequate	10-7-98	N/A
	Type III			1	Adequate	12-31-99	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	06-27-95	N/A
	Type III			1	Adequate	05-22-00	N/A
	Type III			1	Adequate	08-03-01	N/A
	Type III			1	Adequate	09-05-03	N/A
	Type III			1	Adequate	12-20-93	N/A

Chemistry Review Data Sheet

(b) (4)	Type III	(b) (4)	1	Adequate	12-06-01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	23,952	Gepirone Immediate Release Tablets, depression
IND	33,626	Gepirone Sustained Release Formulation (extended release tablets) for depression
IND	(b) (4)	Gepirone HCl (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	02/22/02	Office of Compliance
Pharm/Tox	Pending	10/17/01	Linda Fossom, Ph.D.
Biopharm	N/A	11/20/01	Gerald Fetterly, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
OPDRA	Proposed name not acceptable. No new name proposed.	N/A	David Diwa, Pharm.D.
EA	Categorical Exclusion	2/20/02	Sherita McLamore, Ph.D.

Chemistry Review Data Sheet

Microbiology	N/A	N/A	N/A

Chemistry Assessment Section

The Chemistry Review for NDA 21-164

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-164 is **Not Approvable** from a Chemistry, Manufacturing and Control perspective. On June 15, 2004, the Office of Compliance has indicated that the Organon Inc. Sub Akzona Inc. (West Orange, NJ; CFN #2211109) site will be closing in June 2004 and issued an overall recommendation of WITHHOLD for this application (see appended EER and comment 2 on page 23 of this application). Approval of this application is contingent upon an acceptable recommendation from the Office of Compliance. Accordingly, the applicant will be asked to withdraw this site from the application and to confirm that Organon N.V. (OSS, NL; CFN #9610342) and Pliva USA Inc. (East Hanover, NJ; CFN #2243128) will continue to serve as the release testing facilities for the drug product.

Methods validation is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Gepirone Hydrochloride is a member of the azapirone class of compounds and is indicated for the treatment of patients with major depressive disorder. The drug product, ORG33062 (gepirone hydrochloride) is a new molecular entity and accordingly the applicant claims exclusivity for the drug product. Gepirone was originally developed by Mead Johnson and Bristol Myers Company then later by Fabre-Kramer Pharmaceuticals. In 1998, the applicant obtained the rights to develop and market the drug substance. Gepirone Hydrochloride Extended Release Tablets are available in 20, 40, 60 and 80 mg strengths. They are (b) (4) rectangular shaped biconvex debossed tablets each with similar weights and different colors. (b) (4) The tablet weights range from 375 to 410 mg. Each of the four strengths will be packaged in 30, 100 and 500 count (b) (4) HDPE bottles with a child resistant (b) (4) closures. Additionally, (b) (4).

Chemistry Assessment Section

Gepirone Hydrochloride Extended Release Tablets are supplied as polymorphic (b) (4). The applicant provided identification and testing for the presence of polymorphic (b) (4) and the absence of polymorphic (b) (4). Gepirone Hydrochloride Extended Release Tablets are manufactured (b) (4) The applicant has provided specifications for the drug product, however, the applicant neglected to include a specification for the (b) (4) and the specification for the related substance was broad. Accordingly, the applicant was asked to tighten the related substance specification so that it is more reflective of the data and to include a specification for the (b) (4). The dissolution specification is 1st hour:15-25%; (b) (4); 12th hour 65-86% and 20th hour: NLT 86%. The dissolution specification and all other specifications provided by the applicant are acceptable.

The applicant has requested a 36 month expiration dating for all potencies of the drug product. As indicated in the stability section of this review, the applicant provided 36 months of stability data the 20, 40, 60 and 80 mg **biconvex** tablets. The applicant provides 12 months of long-term and accelerated stability data for the new flat tablets.

Originally, the proposed proprietary name for the drug product was Ariza (Gepirone HCl Extended-Release Tablets) 20 mg, 40 mg, 60 mg and 80 mg. The Office of Post –Marketing Drug Risk Assessment (OPDRA) concluded that Ariza was not an acceptable name for the drug product. On February 9, 2004, the applicant proposed the use of the name VARIZA™ and Variza™ as a trademark name for the drug product.

The applicant references DMF (b) (4) for the synthesis of gepirone hydrochloride. The drug substance is a white to off-white crystalline powder with a melting point of 180°C. The molecular formula for the drug substance is $C_{19}H_{29}N_5O_2 \cdot HCl$ and the molecular weight is 395.93. The synthesis and characterization of the drug substance is described in detail in (b) (4) Type II DMF (b) (4). The DMF was reviewed and had several deficiencies. The holder was advised of the deficiencies and responded on November 27, 2001. The response by the DMF holder was found adequate to support this application.

Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

Gepirone Hydrochloride Extended Release Tablets are being developed for the treatment of depression. The recommended starting dose is 20 mg per day. The applicant indicates that the dose should be increased to 40 mg per day (b) (4) (b) (4) the dose may be increased to a maximum dose of 80 mg per day

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-164 is **Not Approvable** from the chemistry, manufacturing and controls (CMC) standpoint. The Office of Compliance will need to find all sites included in this application acceptable. Additionally, the applicant will need submit a stability protocol for the to-be marketed drug product (see comments 1 and 2, page 22). Previously, the application was considered "Approvable" from a CMC perspective because the Office of Compliance had not made a recommendation on this application. On June 15, 2004, however, the Office of Compliance issued an overall recommendation of **WITHHOLD** because the Organon Inc. Sub Akzona Inc. (West Orange, NJ; CFN #2211109) site will be closing in June 2004.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-164
HFD-120/Division File
HFD-120/PDavid
HFD-120/SMcLamore
HFD-120/TOliver

13 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
6/21/04 11:10:55 AM
CHEMIST

Thomas Oliver
6/21/04 01:06:25 PM
CHEMIST

Chemistry Review Data Sheet

NDA 21-164

Variza™ (Gepirone Hydrochloride) Extended Release Tablet

Organon, Inc.

Sherita D. McLamore, Ph.D.
HFD-120

Chemistry Review Data Sheet

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-164

2. REVIEW # 3

3. REVIEW DATE: April 30, 2004

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	5/18/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	2/15/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon, Inc.
Address:	375 Mount Pleasant Avenue West Orange, NJ 07052
Representative:	Edna Gilvary, Ph.D.
Telephone:	973.325.4627

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Variza
b) Non-Proprietary Name (USAN): Gepirone Hydrochloride
c) Code Name/# (ONDC only): ORG 33062

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 20, 40, 60 and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

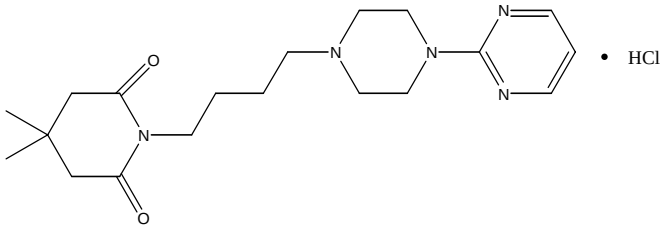
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 3,3-Dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]glutarimide mono-hydrochloride
Molecular Formula: $C_{19}H_{29}N_5O_2$. HCl
Molecular Weight: 395.93



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	1	Adequate	02-5-02	N/A
	Type III			1	Adequate	09-28-00	N/A
	Type III			1	Adequate	09-26-00	N/A
	Type III			1	Adequate	08-25-98	N/A
	Type III			1	Adequate	09-19-00	N/A
	Type III			1	Adequate	10-7-98	N/A
	Type III			1	Adequate	12-31-99	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	06-27-95	N/A
	Type III			1	Adequate	05-22-00	N/A
	Type III			1	Adequate	08-03-01	N/A
	Type III			1	Adequate	09-05-03	N/A
	Type III			1	Adequate	12-20-93	N/A

Chemistry Review Data Sheet

(b) (4)	Type III	(b) (4)	1	Adequate	12-06-01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	23,952	Gepirone Immediate Release Tablets, depression
IND	33,626	Gepirone Sustained Release Formulation (extended release tablets) for depression
IND	(b) (4)	Gepirone HCl (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	02/22/02	Office of Compliance
Pharm/Tox	Pending	10/17/01	Linda Fossom, Ph.D.
Biopharm	N/A	11/20/01	Gerald Fetterly, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
OPDRA	Proposed name not acceptable. No new name proposed.	N/A	David Diwa, Pharm.D.
EA	Categorical Exclusion	2/20/02	Sherita McLamore, Ph.D.

Chemistry Review Data Sheet

Microbiology	N/A	N/A	N/A

Chemistry Assessment Section

The Chemistry Review for NDA 21-164

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-164 is approvable from a Chemistry, Manufacturing and Control perspective. The applicant has adequately responded to all CMC comments but the Office of Compliance will need to find all sites acceptable (overall recommendation is still pending).

Methods validation is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Gepirone Hydrochloride is a member of the azapirone class of compounds and is indicated for the treatment of patients with major depressive disorder. The drug product, ORG33062 (gepirone hydrochloride) is a new molecular entity and accordingly the applicant claims exclusivity for the drug product. Gepirone was originally developed by Mead Johnson and Bristol Myers Company then later by Fabre-Kramer Pharmaceuticals. In 1998, the applicant obtained the rights to develop and market the drug substance. Gepirone Hydrochloride Extended Release Tablets are available in 20, 40, 60 and 80 mg strengths. They are (b) (4) rectangular shaped biconvex debossed tablets each with similar weights and different colors. (b) (4) The tablet weights range from 375 to 410 mg. Each of the four strengths will be packaged in 30, 100 and 500 count (b) (4) HDPE bottles with a child resistant (b) (4) closures. Additionally, (b) (4)

Gepirone Hydrochloride Extended Release Tablets are supplied as polymorphic (b) (4) The applicant provided identification and testing for the presence of polymorphic (b) (4) and the absence of polymorphic (b) (4) Gepirone Hydrochloride Extended Release Tablets are manufactured (b) (4)

Chemistry Assessment Section

(b) (4) The applicant has provided specifications for the drug product, however, the applicant neglected to include a specification for the (b) (4) and the specification for the related substance was broad. Accordingly, the applicant was asked to tighten the related substance specification so that it is more reflective of the data and to include a specification for the (b) (4). The dissolution specification is 1st hour:15-25%; (b) (4) 12th hour 65-86% and 20th hour: NLT 86%. The dissolution specification and all other specifications provided by the applicant are acceptable.

The applicant has requested a 36 month expiration dating for all potencies of the drug product. As indicated in the stability section of this review, the applicant provided 36 months of stability data the 20, 40, 60 and 80 mg **biconvex** tablets. The applicant provides 12 months of long-term and accelerated stability data for the new flat tablets.

Originally, the proposed proprietary name for the drug product was Ariza (Gepirone HCl Extended-Release Tablets) 20 mg, 40 mg, 60 mg and 80 mg. The Office of Post –Marketing Drug Risk Assessment (OPDRA) concluded that Ariza was not an acceptable name for the drug product. On February 9, 2004, the applicant proposed the use of the name VARIZA™ and Variza™ as a trademark name for the drug product.

The applicant references DMF (b) (4) for the synthesis of gepirone hydrochloride. The drug substance is a white to off-white crystalline powder with a melting point of 180°C. The molecular formula for the drug substance is $C_{19}H_{29}N_5O_2 \cdot HCl$ and the molecular weight is 395.93. The synthesis and characterization of the drug substance is described in detail in (b) (4) Type II DMF (b) (4) The DMF was reviewed and had several deficiencies. The holder was advised of the deficiencies and responded on November 27, 2001. The response by the DMF holder was found adequate to support this application.

Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

Gepirone Hydrochloride Extended Release Tablets are being developed for the treatment of depression. The recommended starting dose is 20 mg per day. The applicant indicates that the dose should be increased to 40 mg per day (b) (4) (b) (4) the dose may be increased to a maximum dose of 80 mg per day

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-164 is **Approvable** from the chemistry, manufacturing and controls (CMC) standpoint. The Office of Compliance will need to find all sites acceptable (currently OC's decision is pending). Additionally, the applicant will need submit a stability protocol for the to-be marketed drug product (see comment 1, page 42). Previously, the application was considered "Approvable" from a CMC perspective because of the following: an inadequate packaging DMF, inadequate drug product specifications and an inadequate post-approval stability protocol. These deficiencies were communicated to the applicant in the March 15, 2002 "Not Approvable" letter. The applicant has adequately responded to all of those CMC deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-164
HFD-120/Division File
HFD-120/PDavid
HFD-120/SMcLamore
HFD-120/TOliver

31 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
6/14/04 02:51:29 PM
CHEMIST

Thomas Oliver
6/14/04 02:56:16 PM
CHEMIST

NDA 21-164

Gepirone Hydrochloride Extended Tablet

Organon, Inc.

Sherita D. McLamore
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-164

2. REVIEW # 2

3. REVIEW DATE: February 26, 2002

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	5/18/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	2/15/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon, Inc.
Address:	375 Mount Pleasant Avenue West Orange, NJ 07052
Representative:	Edna Gilvary, Ph.D.
Telephone:	973.325.4627

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Gepirone Hydrochloride
c) Code Name/# (ONDC only): ORG 33062

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Extended Release Tablet

12. STRENGTH/POTENCY: 20, 40, 60 and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

_____SPOTS product – Form Completed

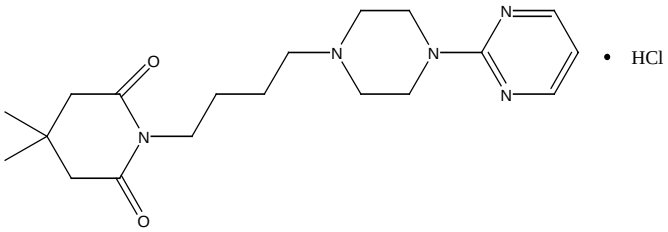
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 2, 6-piperidinedione-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl] butyl]-monohydrochloride

Molecular Formula: $C_{19}H_{29}N_5O_2$. HCl

Molecular Weight: 395.93



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	1	Adequate	02-5-02	N/A
	Type III			1	Adequate	09-28-00	N/A
	Type III			1	Adequate	09-26-00	N/A
	Type III			1	Adequate	08-25-98	N/A
	Type III			1	Adequate	09-19-00	N/A
	Type III			1	Adequate	10-7-98	N/A
	Type III			1	Adequate	12-31-99	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	06-27-95	N/A
	Type III			1	Adequate	05-22-00	N/A
	Type III			1	Adequate	08-03-01	N/A
	Type III			1	Inadequate	04-8-98	N/A
	Type III			1	Adequate	12-20-93	N/A
	Type III			1	Adequate	12-06-01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	23,952	Gepirone Immediate Release Tablets, depression
IND	33,626	Gepirone Sustained Release Formulation (extended release tablets) for depression
IND	(b) (4)	Gepirone HCl (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	02/22/02	Compliance
Pharm/Tox	Pending	10/17/01	Linda Fossom, Ph.D.
Biopharm	N/A	11/20/01	Gerald Fetterly, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
OPDRA	Proposed name not acceptable. No new name proposed.	N/A	David Diwa, Pharm.D.
EA	Categorical Exclusion	2/20/02	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

OGD:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

REVIEWS			
Microbiology	N/A	N/A	N/A
EES	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	N/A	N/A	N/A
Bioequivalence	N/A	N/A	N/A
EA	N/A	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-164

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-164 is approvable from a Chemistry, Manufacturing and Control perspective because of the deficient drug packaging drug master file (DMF), inadequate drug product specifications and inadequate post-approval stability protocol. The applicant will be sent a list of the deficiencies in the FDA Action Letter.

Methods validation is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Gepirone Hydrochloride is a member of the azapirone class of compounds and is indicated for the treatment of patients with major depressive disorder. The drug product, ORG33062 (gepirone hydrochloride) is a new molecular entity and accordingly the applicant claims exclusivity for the drug product. Gepirone was originally developed by Mead Johnson and Bristol Myers Company then later by Fabre-Kramer Pharmaceuticals. In 1998, the applicant obtained the rights to develop and market the drug substance. Gepirone Hydrochloride Extended Release Tablets are available in 20, 40, 60 and 80 mg strengths. They are (b) (4) rectangular shaped biconvex debossed tablets each with similar weights and different colors. (b) (4) tablet weights range from 375 to 410 mg. Each of the four strengths are packaged in 30, 100 and 500 count (b) (4) HDPE bottles with a child resistant (b) (4) closure. Additionally, (b) (4)

Gepirone Hydrochloride Extended Release Tablets are supplied as polymorphic (b) (4) The applicant provided identification and testing for the presence of polymorphic (b) (4) and the absence of polymorphic (b) (4). Gepirone Hydrochloride Extended Release Tablets are manufactured (b) (4)

(b) (4) The applicant has provided specifications for the drug product however, the applicant neglected to include a specification for the (b) (4) and the specification for the related substance was broad. Accordingly, the applicant was asked to tighten the related substance specification so that it is more reflective of the data and to include a specification for the (b) (4). The dissolution specification is 1st hour:15-25% (b) (4) 12th hour 65-86% and 20th hour: NLT (b) (4)%. The dissolution specification and all other specifications provided by the applicant are reasonable and acceptable

The applicant has requested a 36 month expiration dating for all potencies of Gepirone Hydrochloride Extended Release Tablets in bottles (b) (4) As indicated in the stability section of this review, the applicant provided up to 24 months of primary stability data for the 20 mg tablets and 6 months of data for the 40, 60 and 80 mg tablets. The applicant has not provided adequate stability data to support a 36 month expiry for the higher potencies. The applicant will be granted a 36 month shelf life for the 20 mg tablets and based on the stability data included in this application the applicant will be granted a 12 month shelf life for the 40, 60 and 80 mg tablets.

The proposed proprietary name for the drug product is Ariza (Gepirone HCl Extended-release Tablets) 20 mg, 40 mg, 60 mg and 80 mg. The Office of Post –Marketing Drug Risk Assessment (OPDRA) does not recommend the use of Ariza based on information that is currently available.

The applicant references DMF (b) (4) for the synthesis of gepirone hydrochloride. The drug substance is a white to off white crystalline powder with a melting point of 180°C. The molecular formula for the drug substance is $C_{19}H_{29}N_5O_2 \cdot HCl$ and the molecular weight is 395.93. The synthesis of the drug substance is described in detail in (b) (4) Type II DMF (b) (4) The DMF was reviewed and had several deficiencies. The holder was advised of the deficiencies and responded on November 27, 2001. The response by the DMF holder was adequate to support this application.

B. Description of How the Drug Product is Intended to be Used

Gepirone Hydrochloride Extended Release Tablets are being developed for the treatment of depression. The recommended starting dose is 20 mg per day. The applicant indicates that the dose should be increased to 40 mg per day (b) (4) the dose may be increased to a maximum dose of 80 mg per day (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-164 is **Approvable** from the chemistry, manufacturing and controls (CMC) standpoint. Previously, the application was considered "Not Approvable" from a CMC perspective because, Oraganon of West Orange , NJ (CFN 2211109), which is the proposed site for stability and release testing of the drug product, received a withhold recommendation from the Office of Compliance. The applicant has withdrawn that site and submitted a new site for stability testing. The new site, Organon NV (CFN 9610342), was submitted to the Office of Compliance through EES on February 15, 2002 and found acceptable on February 22, 2002.

The "Approvable" recommendation is based on the following remaining outstanding chemistry issues: an inadequate packaging DMF, inadequate drug product specifications and an inadequate post-approval stability protocol. These deficiencies are listed at the end of this review and should be communicated to the applicant. Before NDA 21-164 can be approved from the CMC standpoint, the applicant should address all of the deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
HPatel (TL)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-164
HFD-120/Division File
HFD-120/PDavid
HFD-120/SMcLamore
HFD-120/HPatel

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
2/26/02 12:09:10 PM
CHEMIST

Hasmukh Patel
2/26/02 12:15:10 PM
CHEMIST

NDA/ANDA 21-164

Gepirone Hydrochloride Extended Tablet

Organon, Inc.

Sherita D. McLamore
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-164

2. REVIEW # 1

3. REVIEW DATE: 01/31/02

4. REVIEWER: Sherita McLamore

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	5/18/01
Amendment	

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon, Inc.
Address:	375 Mount Pleasant Avenue West Orange, NJ 07052
Representative:	Edna Gilvary, Ph.D.
Telephone:	973.325.4627

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Gepirone Hydrochloride
c) Code Name/# (ONDC only): ORG 33062

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Extended Release Tablet

12. STRENGTH/POTENCY: 20, 40, 60 and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

_____SPOTS product – Form Completed

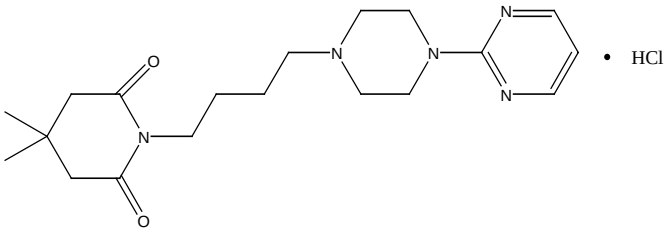
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 2, 6-piperidinedione-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl] butyl]-monohydrochloride

Molecular Formula: $C_{19}H_{29}N_5O_2$. HCl

Molecular Weight: 395.93



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	1	Adequate	02-5-02	N/A
	Type III			1	Adequate	09-28-00	N/A
	Type III			1	Adequate	09-26-00	N/A
	Type III			1	Adequate	08-25-98	N/A
	Type III			1	Adequate	09-19-00	N/A
	Type III			1	Adequate	10-7-98	N/A
	Type III			1	Adequate	12-31-99	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	01-04-00	N/A
	Type III			1	Adequate	06-27-95	N/A
	Type III			1	Adequate	05-22-00	N/A
	Type III			1	Adequate	08-03-01	N/A
	Type III			1	Inadequate	04-8-98	N/A
	Type III			1	Adequate	12-20-93	N/A
	Type III			1	Adequate	12-06-01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	23,952	Gepirone Immediate Release Tablets, depression
IND	33,626	Gepirone Sustained Release Formulation (extended release tablets) for depression
IND	(b) (4)	Gepirone HCl (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Withhold	1/28/02	Compliance
Pharm/Tox	N/A	10/17/01	Linda Fossom, Ph.D.
Biopharm	N/A	11/20/01	Gerald Fetterly, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph. D.
OPDRA	Proposed name not acceptable. No new name proposed.	N/A	David Diwa, Pharm.D.
EA	Categorical Exclusion	2/20/02	Sherita McLamore, Ph. D.
Microbiology	N/A	N/A	N/A

OGD:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

REVIEWS			
Microbiology	N/A	N/A	N/A
EES	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	N/A	N/A	N/A
Bioequivalence	N/A	N/A	N/A
EA	N/A	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-164

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-164 is not approvable because of the CGMP issues with respect to the drug product stability testing site (withhold recommendation), deficient drug packaging drug master file (DMF), inadequate drug product specifications and inadequate post-approval stability protocol. The applicant will be sent a list of deficiencies in the FDA Action Letter.

Methods validation will be submitted after all CMC deficiencies have been addressed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Gepirone Hydrochloride is a member of the azapirone class of compounds and is indicated for the treatment of patients with major depressive disorder. The drug product, ORG33062 (gepirone hydrochloride) is a new molecular entity and accordingly the applicant claims exclusivity for the drug product. Gepirone was originally developed by Mead Johnson and Bristol Myers Company then later by Fabre-Kramer Pharmaceuticals. In 1998, the applicant obtained the rights to develop and market the drug substance. Gepirone Hydrochloride Extended Release Tablets are available in 20, 40, 60 and 80 mg strengths. They are (b) (4) rectangular shaped biconvex debossed tablets each with similar weights and different colors. (b) (4) tablet weights range from 375 to 410 mg. Each of the four strengths are packaged in 30, 100 and 500 count (b) (4) HDPE bottles with a child resistant (b) (4) closure. Additionally, (b) (4)

Gepirone Hydrochloride Extended Release Tablets are supplied as polymorphic (b) (4) The applicant provided identification and testing for the presence of polymorphic (b) (4) and the absence of polymorphic (b) (4) Gepirone Hydrochloride Extended Release Tablets are manufactured (b) (4)

(b) (4) The applicant has provided specifications for the drug product however, the applicant neglected to include a specification for the (b) (4) and the specification for the related substance was broad. Accordingly, the applicant was asked to tighten the related substance specification so that it is more reflective of the data and to include a specification for the (b) (4). The dissolution specification is 1st hour:15-25%; (b) (4) 12th hour 65-86% and 20th hour: NLT (b) (4)%. The dissolution specification and all other specifications provided by the applicant are reasonable and acceptable

The applicant has requested a 36 month expiration dating for all potencies of Gepirone Hydrochloride Extended Release Tablets in bottles (b) (4) As indicated in the stability section of this review, the applicant provided up to 24 months of primary stability data for the 20 mg tablets and 6 months of data for the 40, 60 and 80 mg tablets. The applicant has not provided adequate stability data to support a 36 month expiry for the higher potencies. The applicant will be granted a 36 month shelf life for the 20 mg tablets and based on the stability data included in this application the applicant will be granted a 12 month shelf life for the 40, 60 and 80 mg tablets.

The proposed proprietary name for the drug product is Ariza (Gepirone HCl Extended-release Tablets) 20 mg, 40 mg, 60 mg and 80 mg. The Office of Post –Marketing Drug Risk Assessment (OPDRA) does not recommend the use of Ariza based on information that is currently available.

The applicant references DMF (b) (4) for the synthesis of gepirone hydrochloride. The drug substance is a white to off white crystalline powder with a melting point of 180°C. The molecular formula for the drug substance is $C_{19}H_{29}N_5O_2 \cdot HCl$ and the molecular weight is 395.93. The synthesis of the drug substance is described in detail in (b) (4) Type II DMF (b) (4). The DMF was reviewed and had several deficiencies. The holder was advised of the deficiencies and responded on November 27, 2001. The response by the DMF holder was adequate to support this application.

B. Description of How the Drug Product is Intended to be Used

Gepirone Hydrochloride Extended Release Tablets are being developed for the treatment of depression. The recommended starting dose is 20 mg per day. The applicant indicates that the dose should be increased to 40 mg per day (b) (4) the dose may be increased to a maximum dose of 80 mg per day (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-164 is Not Approvable from the chemistry, manufacturing and controls (CMC) standpoint. The "Not Approvable" recommendation is based on the following major chemistry issue:

- 21CFR210.1(b) Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General states:

  The failure to comply with any regulations set forth in this part and in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as person who is responsible for the failure to comply, shall be subject to regulatory action.

Before NDA 21-164 can be approved for CMC, the proposed site for stability and release testing of the drug product should receive an acceptable recommendation from the Office of Compliance. Alternatively, the applicant can withdraw the Organon, Inc. in West Orange, NJ facility from their application and propose a new acceptable site for stability testing. Other deficiencies in the application include an inadequate packaging DMF, inadequate drug product specifications and an inadequate post-approval stability protocol.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
HPatel (TL)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-164
HFD-120/Division File
HFD-120/PDavid
HFD-120/SMcLamore
HFD-120/HPatel

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
2/22/02 12:22:35 PM
CHEMIST

Hasmukh Patel
2/22/02 12:34:36 PM
CHEMIST