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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207-920
Supporting document/s:	S000
Applicant's letter date:	February 6, 2015
CDER stamp date:	February 6, 2015 (eCTD format)
Product:	Nexium® 24HR (Esomeprazole Magnesium) Delayed-Release 20 mg Tablets
Indication:	Treatment of frequent heartburn in adults
Applicant:	AstraZeneca & Pfizer Inc.
Review Division:	Division of Nonprescription Drug Products
Primary Reviewer:	Wafa Harrouk, PhD
Secondary Reviewer:	Paul Brown, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Jeffrey Buchanan, RPM

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207-920 are owned by Pfizer for which the above mentioned sponsor has obtained a written right of reference.
Any information or data necessary for approval of NDA 207-920 that the sponsor does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 207-920.

Executive Summary

This fully electronic[1] New Drug Application (NDA 207-920) is a 505(b)(1) application which has been submitted by Astra Zeneca & Pfizer Inc. to obtain marketing approval for the over the counter (OTC) use of Nexium® 24HR (Esomeprazole Magnesium) Delayed-Release 20 mg Tablets (once daily for 14 days; treatment course may be repeated every 4 months) for the relief of frequent heartburn which occurs 2 or more days a week in adults 18 years of age or older.

The reference drug is Nexium 24HR® Delayed-Release Capsules, approved under NDA 204-655 and manufactured by AZ.

No new nonclinical studies were conducted for this NDA. The sponsor intends to cross-reference the nonclinical section of this NDA to the summary information provided in the original prescription Nexium 24HR® Delayed-Release Capsules (NDA 204-655, Sequence 0002, Section 2.4). Nonclinical data presented in NDA 204-655, in turn, relied on the nonclinical overview from prescription Nexium 24HR® Delayed-Release Capsules (NDA 21-153).

A Module 4 was not included in this NDA since no new nonclinical studies were conducted.

RECOMMENDATIONS

Approvability: No Pharmacology/Toxicology (pharm/tox) issues were identified for this NDA. This NDA can be approved from the pharm/tox perspective.

Comments to be conveyed to the sponsor: None

OVERVIEW & REGULATORY HISTORY

Esomeprazole has been studied extensively in animal and human studies and is available on the US market as both prescription (20 mg/day & 40 mg/day) and as OTC (20 mg) drug products. The current Nonclinical Overview for esomeprazole tablets

[1] This NDA was submitted in accordance with the electronic Common Technical Document (eCTD)

cross-references the Nonclinical Overview for Nexium (esomeprazole magnesium 22.3 mg) Delayed-Release Capsules approved under NDA 204-655, Section 2.4.

DRUG INFORMATION

Relevant INDs, NDAs, BLAs and DMFs

The original nonclinical summaries and reports referenced in the NDA include:

- NDA 204-655 (SEQ. 0002); Nexium 24 HR Delayed-Release Capsules;
- NDA 21-689; Nexium® IV; (esomeprazole sodium) for Injection;
- NDA 22-101; Nexium® (esomeprazole magnesium) For Delayed-Release Oral Suspension

Drug Formulation

The active ingredient, esomeprazole magnesium trihydrate, (b) (4)

(b) (4)

Composition of Esomeprazole Magnesium Delayed Release Tablet

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
Active [a]				
Esomeprazole magnesium trihydrate (corresponding to esomeprazole 20 mg)	Active	USP	22.3	(b) (4)
Excipients [a]				
Cellulose, microcrystalline	(b) (4)	NF		(b) (4)
Crospovidone (b) (4)		NF		
Glyceryl monostearat (b) (4)		NF		
Hydroxypropyl cellulose		NF		
Hypromellose		USP		
Magnesium stearate		NF		
Methacrylic acid (b) (4) copolymer		NF		

[redacted]	[redacted]	In-House	[redacted]	
Polysorbate 80		NF		
Sodium stearyl fumarate		NF		
[redacted]		NF		
[redacted] Paraffin		NF		
Talc		USP		
Triethyl citrate		NF		
[redacted]		USP	N/A	- -
		USP	N/A	- -

There are no novel excipients used in the manufacture of Esomeprazole magnesium DRT. The only noncompendial excipient is [redacted]; which is covered under [redacted] DMF [redacted] a Letter of Authorization for reference to this DMF is included in the application. A description of the [redacted] is described below.

Composition of [redacted]

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
D&C Red No. 27 [redacted] Aluminum Lake	[redacted]	[redacted]		[redacted]
FD&C Blue 2 [redacted] Aluminum Lake				
FD&C Red No. 40 [redacted] Aluminum Lake				
Hypromellose		USP		
[redacted]		In-House		
Mica		[redacted]		
Titanium dioxide		USP		
Polyethylene glycol		NF		
[redacted]		USP		

The Quality reviewer (Dr. Kasliwal) reviewed the subcomponents of [redacted] and concluded that the ingredients used in [redacted] are either compendial or conform to appropriate Code of Federal Regulations (CFR). Specifically, FD&C Red No. 27 [redacted] (CAS Reg. No. [redacted]) conforms to manufacturing, specifications, labeling and certification per 21CFR [redacted]; FD&C Blue 2 conforms to manufacturing, specifications, labeling and certification per 21CFR [redacted] FD&C Red No. 40 conforms to manufacturing, specifications, labeling and certification per 21CFR [redacted].

(b) (4) conforms to 21 CFR (b) (4). According to 21 CFR (b) (4) "… (b) (4) percent, by weight, of the final drug product…". (b) (4) component of the (b) (4) applied to Esomeprazole delayed-release tablets is present at a theoretical level of (b) (4)% by weight, almost a factor of (b) (4) than the CFR limit.

NONCLINICAL SUMMARY

No new nonclinical pharmacology or toxicology data were conducted for Nexium® 24HR (Esomeprazole Magnesium) Delayed-Release 20 mg Tablets. Module 4 for nonclinical data was not included in this submission.

COMMENTS ON IMPURITIES AND DEGRADANTS OF CONCERN

No new impurities were identified for this drug product

INTEGRATED OVERVIEW AND CONCLUSIONS

The sponsor is relying on previously submitted nonclinical information which they own and the Agency's previous findings of safety of Nexium (omeprazole magnesium DRT, 22.3 mg) to support its approval in the OTC setting. Based on the nonclinical evidence available and the clinical history of the prescription and OTC omeprazole products, there are no novel safety concerns from the nonclinical perspective that would prevent the approvability of this NDA under the recommended conditions of use.

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/s/

WAFA HARROUK
10/27/2015

PAUL C BROWN
10/27/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA

Applicant: Pfizer Inc.

NDA#: 207-920

Stamp date: This fully electronic document was submitted on February 6, 2015

Drug name: Esomeprazole Magnesium 22.3 mg Delayed-Release Tablets (DRT)

NDA type: 505 (b)(1)

Indication: To treat frequent heartburn which occurs 2 or more days a week in adults 18 Years of age and older

Background: The nonclinical section for this NDA cross-references the summary of information provided in the Nonclinical Overview for Nexium 24HR Delayed-Release Capsules (NDA 204655; Sequence 0002, Section 2.4). NDA 204655 was originally approved for over the counter (OTC) market on March 28, 2014 and is also held by Pfizer. The nonclinical aspects were discussed with the sponsor at a pre-NDA meeting (Pre-IND 118964 Meeting, Jan 28, 2014).

Relevant INDs/NDAs:
Esomeprazole magnesium trihydrate, NEXIUM 24HR Capsules, was originally approved under NDA 21-153 and is cross-referenced to the original NDA.

Formulation
The active ingredient, esomeprazole magnesium trihydrate, (b) (4)

(b) (4)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA

Composition of Esomeprazole Magnesium Delayed Release Tablet

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
Active [a]				
Esomeprazole magnesium trihydrate (corresponding to esomeprazole 20 mg)	Active	USP	22.3	(b) (4)
Excipients [a]				
Cellulose, microcrystalline	(b) (4)	NF	(b) (4)	
Crospovidone (b) (4)		NF		
Glyceryl monostearate (b) (4)		NF		
Hydroxypropyl cellulose		NF		
Hypromellose		USP		
Magnesium stearate		NF		
Methacrylic acid (b) (4) copolymer (b) (4)		NF		
(b) (4)		In-House		
Polysorbate 80		NF		
Sodium stearyl fumarate		NF		
(b) (4)		NF		
(b) (4) Paraffin		NF		
Talc		USP		
Triethyl citrate		NF		
(b) (4)		USP	N/A	- -
		USP	N/A	- -

[a] The normal quantities listed are theoretical and based on a yield corresponding to 100%.
[b] The amount of ingredient is expressed on a (b) (4) .Methacrylic acid (b) (4) copolymer (b) (4) polysorbate 80.
The amount of sucrose (b) (4)
[e] (b) (4)
N/A; Not applicable

Inactive ingredients: There are no novel excipients used in the manufacture of Esomeprazole magnesium DRT. The only noncompendial excipient is (b) (4) which is covered under (b) (4) DMF (b) (4); a Letter of Authorization for reference to this DMF is included in the application. A description of the (b) (4) is described below.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA

Composition of [redacted] Esomeprazole Magnesium Delayed Release Tablet

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
D&C Red No. 27 [redacted] Aluminum Lake	[redacted]	[redacted]		[redacted]
FD&C Blue 2 [redacted] Aluminum Lake				
FD&C Red No. 40 [redacted] Aluminum Lake				
Hypromellose		USP		
[redacted]		In-House		
Mica		[redacted]		
Titanium dioxide		USP		
Polyethylene glycol		NF		
[redacted]		USP		

Nonclinical information:
All nonclinical aspects were obtained from previous NDA submissions. The original prescription Nexium 24HR Delayed-Release Capsules' nonclinical section (NDA 21-153, February 2001) was used for the Nonclinical Overview in Nexium 24HR Delayed-Release Capsules NDA (204655 (SEQ. 0002), Section 2.4).
The original summaries/reports referenced are listed in:

- NDA 204655 (SEQ. 0002); Nexium24 HR Delayed-Release Capsules
- NDA 21-689; Nexium® IV (esomeprazole sodium) for Injection
- NDA 22-101; Nexium® (esomeprazole magnesium) For Delayed-Release Oral Suspension

A Module 4 was not included since no new nonclinical studies were conducted.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA

On **initial** overview of the NDA application, this 505 (b) (1) submission does not seem to have any outstanding pharmacology/toxicology issues.

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	x		
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	x		No new nonclinical studies were requested for this NDA. This is a 505(b)(1) where the sponsor is referring to nonclinical previously submitted in NDA 204655 and other NDAs held by this applicant.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			N/A
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

To be communicated in the 74-day letter to the sponsor:
The safety profile of the inactive ingredient, (b) (4), will be assessed during the review cycle. There are no other nonclinical review issues to be raised at the time of filing of this NDA.

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/s/

WAFA HARROUK
03/26/2015

PAUL C BROWN
03/26/2015