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APPLICATION NUMBER:

209089Orig1s000
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NON-CLINICAL 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:	209089 and 209090
Supporting document/s:	2 and 2
Applicant's letter date:	31 March 2016
CDER stamp date:	31 March 2016
Product:	Xyzal Allergy 24HR Tablets, 5 mg (209089) and Children's Xyzal Allergy 24HR Oral Solution, 2.5 mg/5 mL (209090) (levocetirizine dihydrochloride)
Indication:	Allergic rhinitis
Applicant:	UCB, Inc. 1950 Lake Park Drive Smyrna, GA 30080 Sanofi US Services, Inc., Agent
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
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1 Executive Summary

1.1 Introduction

The 505(b)(2) NDAs 209089 and 209090 propose partial Rx-to-OTC switches for, respectively, XYZAL 5 mg tablets (levocetirizine dihydrochloride) approved under NDA 022064 (25 May 2007) and XYZAL 2.5 mg/5 mL oral solution approved under NDA 022157 (28 January 2008). The Sponsor proposes [redacted] (b) (4) in the nonprescription treatment of the symptoms of hay fever or other upper respiratory allergies in adults and children 2 years of age and older. The chronic idiopathic urticaria indication will remain prescription only.

1.2 Brief Discussion of Nonclinical Findings

No original data were included in the submission. All nonclinical pharmacology and toxicology data support for the applications is provided by way of cross reference to the Sponsor's original applications for the corresponding, identical prescription drug products and to the Agency's previous determinations of safety and efficacy for the related drug product, cetirizine HCl (NDA 019835). From a nonclinical perspective, these data are both sufficient and adequate to support the proposed Rx-to-OTC switch applications as approvable.

1.3 Recommendations

1.3.1 Approvability: Approvable

1.3.2 Additional Non Clinical Recommendations: None

2 Drug Information

2.1 Drug

CAS Registry Number: 130018-87-0

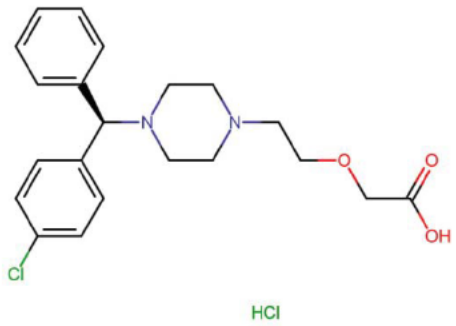
Generic Name: Levocetirizine dihydrochloride

Code Name: UCB 28556

Chemical Name: (2-(4-((R)-(4-Chlorophenyl)phenylmethyl)piperazin-1-yl)ethoxy)acetic acid dihydrochloride

Molecular Formula/Molecular Weight: $C_{21}H_{25}ClN_2O_3$•2ClH/461.8

Structure:



Pharmacologic Class: histamine-1 (H1) receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 022064; NDA 022157; NDA 019835; IND 72,233; DMF [redacted]; DMF [redacted]; DMF [redacted]; DMF [redacted]; DMF [redacted]; DMF [redacted]; DMF [redacted]

2.3 Drug Formulation

NDA 209089: Xyzal Allergy 24HR Tablets, 5 mg

The Sponsor provides drug product description and composition information for this product by way of cross reference to NDA 022064 for Xyzal® Tablets, 5 mg (approved 25 May 2007). The levocetirizine dihydrochloride drug product will be supplied as an immediate release, white to off-white, film-coated, oval-shaped scored tablets for oral administration with each tablet containing 5 mg of levocetirizine dihydrochloride (see Sponsor's Table 1 and figure below). The Sponsor states the following with respect to the proposed new OTC drug product:

> "There are no changes except as noted below to the previously approved Chemistry, Manufacturing, and Controls (CMC)/Quality information, including tablet size and shape, drug substance and drug product specifications, drug substance and drug product manufacturers, container closure systems, and expiration dates associated with this prescription-to-nonprescription switch. The proposed NDA does include the following changes:
>
> - inclusion of a debossed tablet (with updated appearance specification)
> - new packaging configurations for HDPE bottles
> - addition of a peel-push aluminum lidding [redacted] to the blister packages
> - and addition of new packaging sites."

Table 1 - Quantitative Composition of Levocetirizine dihydrochloride Tablets, 5 mg

Component	Amount per tablet (mg)	Function	Reference to Standards
Levocetirizine dihydrochloride	5.00	Active ingredient	In house specification
Microcrystalline cellulose	(b) (4)		NF
Colloidal anhydrous silica			NF
Lactose monohydrate			NF
Magnesium stearate			NF
(b) (4)			In house specification
(b) (4)			USP

Proposed Tablet (debossed logo)

NDA 209090: Children's Xyzal Allergy 24HR Oral Solution, 2.5 mg/5 mL

The Sponsor provides drug product description and composition information for this product by way of cross reference to NDA 022157 for Xyzal® Oral Solution, 0.5 mg/mL (approved 28 January 2008). The levocetirizine dihydrochloride drug product will be supplied as an immediate release, oral solution containing 0.5 mg of levocetirizine dihydrochloride per mL of product (see Sponsor's Table 2.1 below). The Sponsor states the following with respect to the proposed new OTC drug product:

> "There are no changes to previously approved Chemistry, Manufacturing, and Controls (CMC)/Quality information, including drug substance and drug product specifications, drug substance and drug product manufacturers and packagers, container closure systems, and expiration dates associated with this prescription-to-nonprescription switch. However, the proposed NDA includes an administration device (dosing cup)."

Table 2:1 Proposed Commercial Formulation for Levocetirizine Dihydrochloride 0.5 mg/mL Oral Solution

Ingredient	Amount per mL (mg)	Function
Levocetirizine dihydrochloride	0.50	Active ingredient
Sodium acetate trihydrate, USP	(b) (4)	
Glacial acetic acid, USP		
Maltitol Solution, NF		
Glycerin (b) (4) USP		
Methylparaben, NF		
Propylparaben, NF		
Saccharin sodium, USP		
Tutti frutti flavor (b) (4)		
Purified water, USP		

2.4 Comments on Novel Excipients

Neither proposed drug product contains novel excipients.

2.5 Comments on Impurities/Degradants of Concern

No changes are proposed from impurity and/or degradant specifications originally approved for the corresponding prescription drug products.

2.6 Proposed Clinical Population and Dosing Regimen

The Sponsor proposes (b) (4) dose in the nonprescription treatment of the symptoms of hay fever or other upper respiratory allergies in adults and children 2 years of age and older. The recommended nonprescription dosing regimen is as follows:

(b) (4)

This dosing regimen and targeted patient population is consistent with that of the corresponding prescription drug products, except that children <2 years of age and the chronic idiopathic urticaria (CIU) indication are excluded from the proposed nonprescription conditions and dosing is no longer recommended to be confined to the evening.

2.7 Regulatory Background

The 505(b)(2) NDAs 209089 and 209090 propose partial Rx-to-OTC switches for, respectively, XYZAL 5 mg tablets (levocetirizine dihydrochloride) approved under NDA 022064 (25 May 2007) and XYZAL 2.5 mg/5 mL oral solution approved under NDA 022157 (28 January 2008). A Type B Pre-IND meeting (PIND 126506 and 126507) was

held on 1 October 2015, during which the Sponsor was informed that, “In general, it is acceptable to cross-reference to previously submitted information” in providing support for the nonclinical safety of the proposed products (Meeting Minutes, 9 November 2015). A second teleconference was held with the Sponsor on 22 December 2015 to discuss possible scenarios for inclusion or not of the CIU, or hives, indication for the proposed OTC products (Internal Meeting Minutes, 13 January 2016). The Sponsor elected not to include the CIU indication in either of the current Rx-to-OTC switch applications.

In addition to the levocetirizine dihydrochloride studies sponsored and conducted by the Sponsor in support of the prescription NDAs, the Sponsor also references the Agency’s prior determinations of the safety and clinical efficacy of ZYRTEC® (cetirizine dihydrochloride) [5 mg and 10 mg tablets in NDA 019835, oral syrup (5 mg/mL) in NDA 020346, and chewable tablets (5 mg and 10 mg) in NDA 021621] (see Section 3 below).

3 Studies Submitted

No nonclinical studies were included in the current submissions for NDA 209089 or NDA 209090. Rather, the Sponsor cross referenced nonclinical data submitted under its own NDA 022064 for the prescription oral tablet levocetirizine dihydrochloride drug product. These same data had previously been referenced by the Sponsor in support of NDA 022157. Pivotal nonclinical data submitted under NDA 022064 have been reviewed previously (see Section 3.3 below) and are only discussed in summary herein. A tabular listing of all nonclinical safety data referenced by the Sponsor is provided in the Sponsor’s Table 1 reproduced in **Appendix 1**.

As noted above, the Sponsor references prior Agency determinations of nonclinical safety under the cetirizine dihydrochloride NDA 019835 as the source for some pivotal nonclinical data, including chronic toxicity studies in rats and dogs, 2-year dietary carcinogenicity studies in rats and mice, and some developmental and reproductive toxicity study data. A specific letter of authorization (LoA) granting the Sponsor rights to reference data contained in NDA 019835 was not included in the current submission. Relevant nonclinical portions of previously approved Zyrtec prescription drug product labeling under NDA 019835 and also for the current prescription Xyzal prescription drug product under NDA 022064 are appended for reference (see **Appendix 2**).

3.3 Previous Reviews Referenced

- NDA 22-064: Pharmacology/Toxicology Review and Evaluation, L.F. Sancilio, PhD, 8 May 2007.
- NDA 22-157: Pharmacology/Toxicology Review and Evaluation, L.F. Sancilio, PhD, 21 August 2007.
- NDA 22-064/S-017 and NDA 22-157/S003: Pharmacology/Toxicology Review and Evaluation, L.F. Sancilio, PhD, 23 July 2009.

11 Integrated Summary and Safety Evaluation

With NDAs 209089 and 209090, the Sponsor proposes partial Rx-to-OTC switches for, respectively, XYZAL 5 mg tablets (levocetirizine dihydrochloride) and XYZAL 2.5 mg/5 mL oral solution. The Sponsor proposes (b) (4) the nonprescription treatment of the symptoms of hay fever or other upper respiratory allergies in adults and children 2 years of age and older. The CIU indication of the prescription products will be excluded from nonprescription use for the time being as will dosing in patients less than two years of age.

Importantly, for both the proposed nonprescription drug products, there are no CMC-related changes from the corresponding prescription drug products, including tablet size and shape, drug substance and drug product specifications, drug substance and drug product manufacturers, and container closure systems.

The proposed dosing regimen for the nonprescription drug products remains identical to that of the corresponding prescription drug products, with the exception that children less than two years of age are excluded from the nonprescription target population and dosing is (b) (4) to be confined to the evening.

In support of the proposed applications, nonclinical data have been provided by way of cross reference to data submitted under the Sponsor's own corresponding prescription NDA 022064 for the oral tablet levocetirizine dihydrochloride drug product, data which were previously referenced in support of NDA 022157 (oral solution). The Sponsor has also referenced the Agency's prior determination of safety of ZYRTEC® (cetirizine dihydrochloride) under NDA 019835 for some pivotal nonclinical safety data. All of these nonclinical data have been reviewed internally by Dr. Lawrence Sancilio, DPARP, and his executive summary is reproduced below.

> "Levocetirizine is the R-enantiomer of cetirizine, a marketed H1 receptor antagonist. In view of this, the long term toxicity, fertility and early developmental and prenatal postnatal developmental toxicity studies with cetirizine represent the toxicity profile of levocetirizine with supplemental bridging toxicity, and embryofetal developmental studies of levocetirizine.
>
> In chronic oral toxicity studies in mice and rats with cetirizine, the liver was the target organ. The liver changes were enzyme induction and fat deposition. In Beagle dogs, targeted organ was the gastrointestinal system. The major clinical sign was emesis. In a dietary carcinogenicity study in rats, cetirizine was not tumorigenic, but the livers showed hypertrophy, vacuolation and fat deposition. In a dietary carcinogenicity study, male mice showed hepatic hypertrophy and benign liver tumors, the latter was due to enzyme induction. In mice, cetirizine did not affect fertility and early development and embryofetal development; in the prenatal and postnatal developmental study, there was lower pup weight. In embryofetal development studies in rats and rabbits, cetirizine was not teratogenic although increased skeletal anomalies/variants were observed

in rabbits. In a 4-week oral toxicity study in rats with levocetirizine, the target organ was the liver. There were hepatic hypertrophy and vacuolation, increased liver weight, induced liver enzymes and fat deposition. Enzyme induction in the rat is not toxicologically relevant. In a 13-week oral toxicity study in rats with levocetirizine alone, the target organ again was the liver. There were hypertrophy and vacuolation, induced liver enzymes and fat deposition. A second 13-week oral toxicity study in rats was a bridging study with levocetirizine and cetirizine. Both compounds at comparable doses produced similar liver effects, increased enzymes, hypertrophy and central fat deposition.

In a 4-week oral toxicity study in dogs, a bridging study was made with cetirizine. At the HD dose, both levocetirizine and cetirizine were toxic putting the animals in a moribund condition which required a reduction in dose. Both compounds induced emesis and produced fecal impaction. The target organ was the gastrointestinal tract.

In a 13-week oral toxicity study in dogs, a bridging study was conducted with cetirizine. Both compounds produced emesis at comparable doses. Based on the toxicity studies in rats and dogs, there was no difference in the toxicity profile of levocetirizine and cetirizine.

Levocetirizine was not mutagenic in the Reverse Bacterial Mutation Assay and not genotoxic in the Mouse Lymphoma, Human Lymphocyte Chromosomal Aberration and Micronucleus Assays.

In a bridging Embryofetal Developmental study in rats and rabbits with levocetirizine and cetirizine, both compounds were not teratogenic although cetirizine did increase skeletal anomalies/variants in rabbits....

Levocetirizine, the R-enantiomer of cetirizine is a potent and competitive H1 receptor antagonist. In vitro H1 receptor binding studies using different tissues [sic], levocetirizine was 2-3 times more potent than cetirizine; in blocking the isolated guinea pig ileum and tracheal response to histamine, levocetirizine was 1-3 times more potent than cetirizine. In the in vivo histamine induced skin wheal assay in mice and rats, orally levocetirizine was 2-4 times more potent than cetirizine."

Dr. Sancilio's review confirms that all required toxicological endpoints have been sufficiently and adequately addressed for levocetirizine and that the data do not identify adverse effects that would raise safety concerns in the OTC environment. Thus, it is concluded that the current applications proposing a switch from prescription to nonprescription status for levocetirizine dihydrochloride oral tablets and solution may be considered approvable from a nonclinical perspective.

12 Appendix/Attachments

Appendix 1

Table 1 - Cross Reference Table of Nonclinical Study Reports from Xyzal® (levocetirizine dihydrochloride) Tablets NDA 22-064 [excerpted from Sponsor]

Section	Report Type	Report Title	Report Number	Page in NDA 22-064 Module 2 – Nonclinical Summary
2.6.1 Introduction - text does not reference specific reports				
2.6.2 Pharmacology Written Summary				
2.6.2.1 Brief Summary - text does not reference specific reports				
2.6.2.2 Primary Pharmacodynamics				
2.6.2.2.1.1	In Vitro Antihistaminic Activity	In Vitro Study of the Capacity of ucb 28556 and ucb 28557 to Inhibit [3H]-Mepyramine Binding to the Cerebral Cortex of Mice	Report RRLE95A0510	17
2.6.2.2.1.2		Binding Characteristics of ucb 28556 and ucb 28557 to Human H1 Histamine Receptors: Comparison with Cetirizine	Report RRLE95M1801	18
2.6.2.2.1.3		Affinity and Selectivity Profile of Cetirizine, ucb 28556 and ucb 28557 for Human H1 Histamine Receptors	Report RRLE96A1901	20
2.6.2.2.1.4		H1 Antagonists: Receptor Affinity Versus Selectivity	Report ADPE03B1704	24
2.6.2.2.1.5		Binding Characteristics of Cetirizine and Levocetirizine to Human H1 Histamine Receptors: Contribution of Lys191 and Thr194	Report ADPE02A3102	26
2.6.2.2.1.6		Binding Characteristics of [3H]-Levocetirizine to Cloned Human H1 Histamine Receptors Expressed in CHO Cells	Report ADPE02E1404	33
2.6.2.2.1.7		Histamine H1-Receptor Activation of Nuclear Factor-κB: Roles for Gβ γ– and GαQ/11 – Subunits in Constitutive and Agonist-Mediated Signaling	Report ADPE02B2701	35
2.6.2.2.1.8		Antihistaminic Properties of ucb 28556 and ucb 28557 Assessed In Vitro in the Guinea-Pig Trachea	Report RRLE92E2004	39
2.6.2.2.1.9		Activity of ucb 28556 and ucb 28557 on the Isolated Guinea-Pig Ileum Contracted by Acetylcholine, Serotonin, Histamine or Nicotine	Report RRLE92E2003	40
2.6.2.2.1.10		Effect of Cetirizine and its Enantiomers on Histamine-Induced Contractions of Isolated Guinea-Pig Trachea	Report RRLE98J2801	41
2.6.2.2.1.11		Antagonism, by Cetirizine and its Enantiomers, of Histamine-Induced Contractions in the Guinea-Pig Ileum	Report RRLE97G1803	42
2.6.2.2.1.12		Histamine H1 Receptor Antagonism by Cetirizine in Isolated Guinea Pig Tissues: Influence of Receptor Reserve and Dissociation Kinetics	Report ADPE03F0305	43

2.6.2.2.1.13	In vivo antihistaminic activity (pulmonary and respiratory effects)	General Behavioural Effects and Antihistaminic Activity of ucb P071 and its Enantiomers (ucb 28556 and ucb 28557)	Report LE88B242 [RXLE93G1202 = Addendum to DE86D142; RXLE94A1703 = Addendum to DE86D143]	51
2.6.2.2.1.14		Effect of ucb 28556 and ucb 28557 on Respiratory Spasms Induced in the Guinea-Pig (Konzett test)	Report RRLE95G1801	52
2.6.2.2.1.15		Pharmacodynamic Kinetics of ucb P071 and its Enantiomers in Histamine-Induced Bronchospasm in Anaesthetized, Curarized Guinea-Pigs	Report RRLE95A0511	53
2.6.2.2.1.16	In vivo antihistaminic activity (cutaneous effects)	General Behavioral Effects and Antihistaminic Activity of ucb P071 and its Enantiomers (ucb 28556 and ucb 28557)	Report LE88B242 [RXLE93G1202 = Addendum to DE86D142; RXLE94A1703 = Addendum to DE86D143]	54
2.6.2.2.1.17		Effect of ucb 28556 and ucb 28557 on the Surface Area of Histamine-Induced Cutaneous Wheals in Mice	Report RRLE95A0509	55
2.6.2.2.1.18		Effect of ucb 28556 and ucb 28557 on the Area of Cutaneous Wheals Induced by Histamine in the Mouse	Report RRLE95E2901	56
2.6.2.2.1.19		Effect of ucb 28556 and ucb 28557 on the Surface Area of Histamine-Induced Cutaneous Wheals in Rats	Report RRLE95A0502; Addendum No. 1 RXLE95A0503	56
2.6.2.2.1.20		Effect of ucb 28556, ucb 28557 and Cetirizine on Surface Area of Histamine-Induced Cutaneous Wheals in Dogs	Report RRLE95A0504; Amendment 1 RXLE00D1002	57
2.6.2.2.1.21		The Effect of ucb 26071 and its Isomers, ucb 28556 and 28557, on Histamine-Induced Cutaneous Reactions in Dogs	Report RRLE95A1202	58
2.6.2.2.1.22		Study of the Effect of ucb 28556 and ucb 28557 on Histamine-Induced Cutaneous Reactions in Dogs	Report RRLE95A0512	59
2.6.2.2.1.23		Anti- Histaminic Activities and General Pharmacological Studies of ucb P026: Metabolite of Cetirizine	Report RXLE94E2705	60

2.6.2.3 Secondary Pharmacodynamics				
2.6.2.3.1	Secondary Pharmacokinetics	Cetirizine and Levocetirizine Inhibit Eotaxin-Induced Eosinophil Transendothelial Migration Through Human Dermal or Lung Microvascular Endothelial Cells	Report ADPE02J0203	61
2.6.2.3.2		H1 Histamine Receptor Mediates Inflammatory Responses in Human Keratinocytes	Report ADPE04L2201	63
2.6.2.3.3		Inhibition by Levocetirizine of VCAM-1 Expression on Human Dermal Endothelial Cells	Report ADPE03K3101	68
2.6.2.3.4		The Effects of Levocetirizine on Histamine- and Cytokine- Induced Up-Regulation of Eotaxin by Endothelial Cells	Report ADPE02G1007	68
2.6.2.4 Safety Pharmacology				
2.6.2.4.1.1	Central Nervous System	Influence of ucb P071 and its Enantiomers, ucb 28556 and ucb 28557, on the General Behavior in Mice (Irwin)	Report LE88B242	69
2.6.2.4.1.2		Effects of ucb 28556 after Intraperitoneal or per os Administration on the General Behavior of the Mouse (Irwin Test)	Report RRLE92E0508, Addendum to RXLE94A1704	69
2.6.2.4.1.3		Study of the Effect of ucb 28556 on Hexobarbital-Induced Loss of Righting Reflex in Mice	Report RRLE95A0505	70
2.6.2.4.1.4		Effects of ucb 28556, ucb 28557 and Cetirizine on Hexobarbital-Induced Loss of Righting Reflex in the Mouse	Report RRLE93D2901	71
2.6.2.4.1.5		ucb 28556: Assessment of Effects on General Activity and Behavior (Irwin Test) in Comparison with ucb P071 in the Rat	Report RRLE99A1104	72
2.6.2.4.1.6		ucb 28556: Assessment of Effects on General Locomotor Activity in Comparison with ucb P071 in the Rat	Report RLE99A1105; Amendment 1 RXLE00A1101	72
2.6.2.4.1.7		ucb 28556: Assessment of Effects on Pentobarbitone Sleeping Time in Comparison with ucb P071 in the Rat	Report RRLE99A1106; Amendment 1 RXLE00A1103	73
2.6.2.4.1.8		Influence of ucb P026 on General Behavior in Mice (Irwin Test)	Report RRLE95C0101	74
2.6.2.4.2.1	Cardiovascular and Respiratory	The Molecular Basis for the Lack of Cardiovascular Side Effects of Cetirizine: Studies on the Human Ether-a-Gogo Related Gene (hERG) Product, a Cardiac K+ Channel	Report RRLE99B1801	74
2.6.2.4.2.2		Effects of Cetirizine on the Delayed K+ Currents in Cardiac Cells: Comparison with Terfenadine	Report ADPE98G0201	75

2.6.2.4.2.3		Comparative Study of Three Antihistaminic Compounds, Cetirizine, ucb 28556 and ucb 28557, on Action Potentials from Canine Cardiac Purkinje Fibres	Report RRLE98H1102	76
2.6.2.4.2.4		The Haemodynamic Effects of ucb 28556 in Anaesthetized Sprague Dawley Rats	Report RRLE95A0507	76
2.6.2.4.2.5		Acute Circulatory Tolerance of Cumulative Intravenous Doses of ucb 28556 in Anaesthetized Dogs	Report RRLE93H0901	77
2.6.2.4.2.6		ucb 28556: Study on the Effects of ucb 28556 on Cardiac Rhythm in a Model of Acquired Long QT Syndrome in Halothane-Anesthetized Dogs	Report RRLE99H1101, Analytical Report RRLE99J0601	78
2.6.2.4.2.7		ucb 28556: Evaluation of Effects on the Cardiovascular and Respiratory Systems in the Anaesthetised Dog Following Intravenous Administration	Report RRLE96K0402, Toxicokinetic Evaluation RRLE96L0801	78
2.6.2.4.2.8		Influence of ucb P026 on Systemic Blood Pressure and Heart Rate in Anaesthetised Rats	Report RRLE95B2701	79
2.6.2.4.3.1	Other	ucb 28556: Assessment of Effects on Gastrointestinal Transit in Comparison with ucb P071 in the Rat	Report RRLE99A1107, Amendment 1 RXLE00A1102	80
2.6.2.5 Pharmacodynamic Drug Interactions - text does not reference specific reports				
2.6.2.6 Discussion and Conclusions - text does not reference specific reports				
2.6.3 Pharmacology Tabulated Summary - text does not reference specific reports				
2.6.4 Pharmacokinetics Written Summary				
2.6.4.1 Brief Summary - text does not reference specific reports				
2.6.4.2 Analytical Methods - text does not reference specific reports				
2.6.4.3 Absorption				
2.6.4.3.1.1	Pharmacokinetic	Metabolism and Pharmacokinetics of [^{14}C]-ucb 28556 in the OFA Rat after Single Administration by Gavage	Report RRLE95H0901	110
2.6.4.3.1.2		ucb 28556- ucb 28557: Comparative Pharmacokinetics in the Beagle Dog	Report LE88B021	111
2.6.4.3.1.2		ucb 28556: Absorption, Distribution, Metabolism and Elimination of 14C-ucb 28556 after Oral Administration in the Beagle Dog	Report RRLE99J1301	112
2.6.4.3.2	Toxicokinetic	ucb 28556 and ucb 28557: Toxicity to Rats by Repeated Oral Administration for 4 Weeks	Report RRLE95C1401 TK Report RRLE92L2502	Module 2, Section 2.6.6.3.1.1, page 219
		ucb 28556: Toxicity to Rats by Repeated Oral Administration for 13 Weeks Followed by a 4-Week Recovery Period	Report RRLE92G0902 TK Report RRLE93B2201	Module 2, Section 2.6.6.3.1.2, page 221
		A Preliminary Study of the Effect of ucb 28556 on the Pregnant Rat Incorporating Toxicokinetics	Reports RRLE92G1001; TK Report RRLE93B0206	Module 2, Section 2.6.6.6.2.1, page 256
		ucb 28556: 13-Week Oral Toxicokinetics Study in the Rat in Comparison with ucb P071	Report RRLE98F0401 TK Report RRLE99G1201	Module 2, Section 2.6.6.3.1.4, page 225
		ucb 28556: A Preliminary Study of the Effect of ucb 28556 on the Pregnant Rabbit: Incorporating Toxicokinetics and Pilot Study of the Effect on Non-pregnant Rabbit	Report RRLE92G0903 TK Report UCB 438 RRLE92M1801 and Amendment 1 RXLE93L3005	Module 2, Section 2.6.6.6.2.3, page 258
		ucb 28556 and ucb 28557. Toxicity to Dogs by Repeated Oral Administration for 4 Weeks	Report RRLE95C2004 TK Report RRLE93A2803	Module 2, Section 2.6.6.3.2.1, page 227
		ucb 28556, ucb 28557 and ucb P071. Toxicity to Dogs by Repeated Oral Administration for 4 Weeks	Report RRLE99J1401 TK Report RRLE95F0202	Module 2, Section 2.6.6.3.2.2, page 230
		ucb 28556. Toxicity to Dogs by Repeated Oral Administration for 13 Weeks	Report RRLE92G1003 TK Report RRLE93D0104	Module 2, Section 2.6.6.3.2.3, page 234
		ucb 28556. Toxicity to Dogs by Repeated Oral Administration for 13 Weeks in Comparison with ucb P071	Report RRLE97F0201 TK Report RRLE97D1502	Module 2, Section 2.6.6.3.2.4, page 235
		One Year Oral Toxicity Study of Cetirizine (ucb P071) in Beagle Dogs	cetirizine NDA 19-835 [a]	Module 2, Section 2.6.6.3.2.5, page 237
2.6.4.4 Distribution				
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2.6.4.4.1.1		[14C]-ucb 28556: Tissue Distribution of Total Radioactivity in the Wistar Rat following Single Oral Administration (QWBA).	Report RRLE99G1401	114
2.6.4.4.1.2		ucb 28556: Absorption, Distribution, Metabolism and Elimination of [14C]-ucb 28556 after Oral Administration in the Beagle Dog	Report RRLE99J1301	115
2.6.4.3.1.2	Volume of Distribution	ucb 28556- ucb 28557: Comparative Pharmacokinetics in the Beagle Dog	Report LE88B021	111
2.6.4.4.2	Protein Binding	Protein Binding was Determined by Equilibrium Dialysis in the Rat (RRLE95H0901), Dog (RRLE99J1301) and Man (RRLE04K2002, RRLE00K3002)	Reports: RRLE95H0901 (rat), RRLE99J1301 (dog), RRLE04K2002 (human), RRLE00K3002 (human)	117

2.6.4.5 Metabolism				
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2.6.4.5.1		ucb 28556, ucb 28557 and Cetirizine. Comparative in Vitro Metabolism in Human Liver Microsomes	Report RRLE99J2001	118
2.6.4.5.2.1	In Vivo	ucb 28556: Identification of Metabolites of [14C]- ucb 28556 after Single Oral Administration to OFA Rats	Report RRLE00C1503	119
2.6.4.5.2.2		ucb 28556: Absorption, Distribution, Metabolism and Elimination of [14C]-ucb 28556 after Oral Administration in the Beagle Dog	Report RRLE99J1301	119
2.6.4.6 Excretion				
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2.6.4.6.1		Metabolism and Pharmacokinetics of [14C]-ucb 28556 in the OFA Rat after Single Administration by Gavage	Report RRLE95H0901	120
2.6.4.6.2		Absorption, Distribution, Metabolism and Elimination of [14C]-ucb 28556 after Oral Administration in the Beagle Dog	Report RRLE99J1301 with Amendment No. 1	121
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2.6.4.9 Discussion and Conclusion				
2.6.5 Pharmacokinetics Tabulated summary - text does not reference specific reports				

2.6.6 Toxicology Written Summary				
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2.6.6.2.3.1	Single Administration Study in the Dog	ucb 28556-ucb 28557. Single Oral Dose Study in Dogs	Reports RRLE92C1202 and Amendment RXLE93L1003; Plasma Concentrations RRLE92G0601	218
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2.6.6.3.1.2		ucb 28556. Toxicity to Rats by Repeated Oral Administration for 13 Weeks Followed by a 4-Week Recovery Period	Reports RRLE92G0902; Pharmacokinetic Monitoring RRLE93B2201	221

2.6.6.3.1.3		ucb 28556. Toxicity to Rats by Repeated Oral Administration for 13 Weeks followed by a 4 Week Recovery Phase in Comparison with ucb P071	Reports RRLE98H2402; Toxicokinetic Evaluation RRLE97E2301; Lymphocyte Subset Counts in the Rat RRLE98H2403	223
2.6.6.3.1.4		ucb 28556. 13 Week Oral Toxicokinetics Study in the Rat in Comparison with ucb P071	Report RRLE98F0401; Toxicokinetic Evaluation RRLE99G1201	225
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2.6.6.3.2.2		ucb 28556, ucb 28557 and ucb P071. Toxicity to Dogs by Repeated Oral Administration for 4 Weeks	Reports RRLE99J1401; Toxicokinetic Evaluation RRLE95F0202	230
2.6.6.3.2.3		ucb 28556. Toxicity to Dogs by Repeated Oral Administration for 13 Weeks.	Reports RRLE92G1003; Pharmacokinetic Monitoring RRLE93D0104	234
2.6.6.3.2.4		ucb 28556. Toxicity to Dogs by Repeated Oral Administration for 13 Weeks in Comparison with ucb P071	Reports RRLE97F0201; Toxicokinetic Evaluation RRLE97D1502	235
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2.6.6.6 Reproductive and Developmental Toxicity				
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2.6.6.6.2.2		A study of the Effect of ucb 28556 on the Pregnancy of the Rat: Incorporating Toxicokinetics	Reports RRLE93F3001; Toxicokinetic Evaluation RRLE94C0902	256
2.6.6.6.2.3		ucb 28556. A Preliminary Study of the Effect of ucb 28556 on the Pregnant Rabbit: Incorporating Toxicokinetics and Pilot Study of the Effect on Non- Pregnant Rabbit	Reports RRLE92G0903; Pharmacokinetic Monitoring UCB 438 RRLE92M1801 and Amendment 1 RXLE93L3005	258
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2.6.6.7 Local Tolerance - text does not reference specific reports				
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2.6.6.8.1	Antigenicity - text does not reference specific reports			
2.6.6.8.2.1	Immunotoxicity	Lymphocyte Subset Counts in the Rats [in: ucb 28556. Toxicity to Rats by Repeated Oral Administration for 13 Weeks followed by a 4 Week Recovery Phase in Comparison with ucb P071]	Report RRLE98H2403	262
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2.6.6.8.7.1.2		ucb P071, ucb 28556 and ucb 28557. Cytotoxicity on Human Lymphocytes Cultured in Vitro after 3 Hours Treatment in the Presence of S9 mix	Report RRLE99C2601	267
2.6.6.8.7.1.3		Cytotoxicity of ucb P071, Levocetirizine and ucb 28557, Terfenadine, Loratadine and Astemizole on Primary Cultures of Rat Hepatocytes	Report RRLE95J0502	268
2.6.6.8.7.2.1	Interference	In Vitro Interference Study of ucb 28556, ucb 28557, and ucb P071 on the Determination of Alkaline Phosphatase and Inorganic Phosphorus in the Plasma of Beagle Dogs	Report RRLE95E1803	269
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[a] No report number was provided in the levocetirizine NDA 22-064; however the levocetirizine NDA 22-064 references the cetirizine NDA 19-835.

[b] In the levocetirizine NDA 22-064, the report cited for the "Prenatal And Postnatal Development, Including Maternal Function" (i.e. 'Seg III') is ARLE00C1001 per section 2.6.6.6.3.1 (page 260) of the Nonclinical Toxicology Written Summary and Table 2.6.7.14A of the Nonclinical Toxicology Tabulated Summary (page 417). Note that Section 2.4.4.6 (page 39) of the Nonclinical Overview refers to this study in error as ARLE00C1006.

Appendix 2

Relevant excerpts from approved prescription labeling for ZYRTEC (cetirizine hydrochloride) (NDA 019835/S-020, approved 4 April 2006) are reproduced below:

ZYRTEC® (cetirizine hydrochloride)
Tablets, Chewable Tablets and Syrup for Oral Use

CLINICAL PHARMACOLOGY

Mechanism of Action: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. In vivo and ex vivo animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. In vitro receptor binding studies have shown no measurable affinity for other than H1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H1 receptors.

Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m2 basis, or approximately 7 times the maximum recommended daily oral dose in infants on a mg/m2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m2 basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m2 basis, or approximately equivalent to the maximum recommended daily oral dose in infants on a mg/m2 basis). The clinical significance of these findings during long-term use of ZYRTEC is not known.

Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and in vivo micronucleus test in rats.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m2 basis).

Pregnancy Category B: In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220 times the maximum recommended daily oral dose in adults on a mg/m2 basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ZYRTEC should be used during pregnancy only if clearly needed.

Nursing Mothers: In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m2 basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one adult patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18 month old pediatric patient who took an overdose of ZYRTEC (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m2 basis, or approximately 40 times the maximum recommended daily oral dose in infants on a mg/m2 basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m2 basis, or approximately 190 times the maximum recommended daily oral dose in infants on a mg/m2 basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

Relevant excerpts from approved (23 June 2016) prescription labeling for XYZAL (levocetirizine dihydrochloride) (NDA 022064) are reproduced below:

XYZAL® (levocetirizine dihydrochloride)
Tablets and Solution for Oral Use

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, XYZAL should be used during pregnancy only if clearly needed.

Teratogenic Effects
In rats and rabbits, levocetirizine was not teratogenic at oral doses approximately 320 and 390, respectively, times the maximum recommended daily oral dose in adults on a mg/m^2 basis.

8.3 Nursing Mothers
No peri- and post-natal animal studies have been conducted with levocetirizine. In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams that was approximately 40 times the maximum recommended daily oral dose in adults on a mg/m^2 basis. Studies in beagle dogs indicated that approximately 3% of the dose of cetirizine was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk, use of XYZAL in nursing mothers is not recommended.

10 OVERDOSAGE
Overdosage has been reported with XYZAL.

Symptoms of overdose may include drowsiness in adults. In children agitation and restlessness may initially occur, followed by drowsiness. There is no known specific antidote to XYZAL. Should overdose occur, symptomatic or supportive treatment is recommended. XYZAL is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

The acute maximal non-lethal oral dose of levocetirizine was 240 mg/kg in mice (approximately 190 times the maximum recommended daily oral dose in adults, approximately 230 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 180 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis). In rats the maximal non-lethal oral dose was 240 mg/kg (approximately 390 times the maximum recommended daily oral dose in adults, approximately 460 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 370 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Levocetirizine, the active enantiomer of cetirizine, is an antihistamine; its principal effects are mediated via selective inhibition of H1 receptors. The antihistaminic activity of levocetirizine has been documented in a variety of animal and human models. In vitro binding studies revealed that levocetirizine has an affinity for the human H1-receptor 2-fold higher than that of cetirizine (Ki = 3 nmol/L vs. 6 nmol/L, respectively). The clinical relevance of this finding is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been performed with levocetirizine. However, evaluation of cetirizine carcinogenicity studies are relevant for determination of the carcinogenic potential of levocetirizine. In a 2-year carcinogenicity study, in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults, approximately 10 times the maximum recommended daily oral dose in children 6 to 11 years of age and approximately 15 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign hepatic tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults, approximately 4 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 6 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis). No increased incidence of benign tumors was observed at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults, equivalent to the maximum recommended daily oral dose in children 6 to 11 years of age and approximately 2 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis). The clinical significance of these findings during long-term use of XYZAL is not known.

Levocetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and in vivo micronucleus test in mice.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the recommended daily oral dose in adults on a mg/m^2 basis).

13.2 Animal Toxicology

Reproductive Toxicology Studies

In rats and rabbits, levocetirizine was not teratogenic at oral doses up to 200 and 120 mg/kg, respectively, (approximately 320 and 390, respectively, times the maximum recommended daily oral dose in adults on a mg/m^2 basis).

In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).

Manufactured for:
UCB, Inc.
Smyrna, GA 30080

XYZAL is a registered trademark of the UCB Group of companies.

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

/s/

DONALD C THOMPSON
12/02/2016

JANE J SOHN
12/02/2016
I concur.

PHARMACOLOGY/TOXICOLOGY
FILING CHECKLIST FOR NDA

NDA Number: 209-089 **Applicant: UCB, Inc.** **Stamp Date: 31 Mar 2016**

Drug Name: Levocetirizine dihydrochloride oral tablets **NDA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
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).	X		
6	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 applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant 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?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY
FILING CHECKLIST FOR 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/m^2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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

/s/

DONALD C THOMPSON
05/18/2016

JANE J SOHN
05/18/2016

PHARMACOLOGY/TOXICOLOGY
FILING CHECKLIST FOR NDA

NDA Number: 209-090 **Applicant: UCB, Inc.** **Stamp Date: 31 Mar 2016**

Drug Name: Levocetirizine dihydrochloride oral solution **NDA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
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).	X		
6	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 applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant 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?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY
FILING CHECKLIST FOR 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/m^2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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

/s/

DONALD C THOMPSON
05/18/2016

JANE J SOHN
05/18/2016