CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209089Orig1s000
209090Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209089	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Xyzal Allergy 24HR Established/Proper Name: levocetirizine dihydrochloride Dosage Form: tablets Strengths: 5 mg		
Applicant: UCB, Inc.		
Date of Receipt: March 31, 2016		
PDUFA Goal Date: January 31, 2016	Action Goal Date (if different):	
RPM: Sherry Stewart		
Proposed Indication(s): Partial RX to OTC switch for the following: Uses: temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: • runny nose • sneezing • itchy, watery eyes • itching of the nose or throat		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Bridge for nonclinical information has been previously established per NDA 22064 and NDA 22157. The pending OTC NDA cross references these approved RX NDAs.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Zyrtec (cetirizine)tablets	NDA 19835	Yes
Zyrtec (cetirizine) oral syrup	NDA 20346	Yes
Zyrtec (cetirizine) chewable tablets	NDA 21621	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:
NDA 20346 Zyrtec (cetirizine hydrochloride) syrup, 5 mg/5 mL

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application is for the L-enantiomer of the active ingredient that is being relied upon, and provides for a partial Rx-to-OTC switch.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☒ YES ☐ NO ☒

Note: the pharmaceutically equivalent products are owned by the sponsor and cross referenced in this application.

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):
Xyzal tablets-NDA 22064
Multiple approved ANDAs.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☒ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6,455,533 for NDA 21621 Zyrtec chewable tablets

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6,455,533

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

November 18, 2016 submission YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *June 27. 2016*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☒

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

/s/

SHERRY A STEWART
01/24/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 209090	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Children's Xyzal Allergy 24HR (proposed) Established/Proper Name: levocetirizine dihydrochloride Dosage Form: oral solution Strengths: 0.5 mg/mL (2.5 mg/5mL)		
Applicant: UCB, Inc.		
Date of Receipt: March 31, 2016		
PDUFA Goal Date: January 31, 2016	Action Goal Date (if different):	
RPM: Sherry Stewart		
Proposed Indication(s): Partial RX to OTC switch for the following: Uses: temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: • runny nose • sneezing • itchy, watery eyes • itching of the nose or throat		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Bridge for nonclinical information has been previously established per NDA 22064 and NDA 22157. The pending OTC NDA cross references these approved RX NDAs.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Zyrtec (cetirizine)tablets	NDA 19835	Yes
Zyrtec (cetirizine) oral syrup	NDA 20346	Yes
Zyrtec (cetirizine) chewable tablets	NDA 21621	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:
NDA 20346 Zyrtec (cetirizine hydrochloride) syrup, 5 mg/5 mL

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application is for the L-enantiomer of the active ingredient that is being relied upon. This application provides for a partial Rx-to-OTC switch.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☒ YES ☐ NO ☒

Note: the pharmaceutically equivalent products are owned by the sponsor and cross referenced in this application.

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):
Xyzal oral solution-NDA 22157
Multiple approved ANDAs.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☒ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6,455,533 for NDA 21621 Zyrtec chewable tablets

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6,455,533

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

November 18, 2016 submission YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *June 27. 2016*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☒

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

/s/

SHERRY A STEWART
01/24/2017

Addendum Labeling Review for Xyzal® Allergy 24HR Tablets

SUBMISSION DATES:	March 31, 2016 and January 9, 2017
NDA/SUBMISSION TYPE:	209089 (Rx-to-OTC switch)
ACTIVE INGREDIENTS:	Levocetirizine dihydrochloride 5 mg
DOSAGE FORM	Tablet
SPONSOR:	Sanofi US Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 Cynthia Psaras, PhD, Director, Global Regulatory Affairs 908-981-4874
REVIEWER:	Karen Livornese, RN, MSN, DNDP/ODE IV
TEAM LEADER:	Steven Adah, Ph.D., DNDP/ODE IV
ASSOCIATE DIRECTOR for LABELING	Ruth E. Scroggs, PharmD, DNDP/ODE IV
REGULATORY PROJECT MANAGER	Sherry Stewart, Project Manager, DNDP/ ODE IV

I. BACKGROUND

This review follows the labeling review dated December 22, 2016 which requested revised labeling for all labels, the subject of this review.

UCB, Inc. and its agent, Sanofi US Services, Inc., submitted on March 31, 2016, an original new drug application (NDA) 209089, under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act). The sponsor proposes a partial switch to market a tablet form of the antihistamine levocertirizine dihydrochloride 5 mg as an over-the-counter (OTC) product for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in children and adults 6 years of age and older. The chronic idiopathic urticarial (CIU) indication is not being switched to nonprescription use at this time. The approved prescription form of Xyzal® (levocetiritzine dihydrochloride) 5mg tablets, NDA 22-064, is used as the

reference listed drug (RLD). The tablet form of certirizine hydrochloride 10 mg is currently approved as an OTC product in NDA 19-835 (Zyretc® Allergy), and is also referenced in this application.

This is a review of the labeling submitted January 9, 2017 in response to the information request sent by the agency on December 28, 2016 and includes recommendations that were communicated to the sponsor. This review, the second of two, amends our December 22, 2016 labeling review. This is a review of the labeling submitted January 9, 2017 and is compared to the labeling submitted on March 31, 2016.

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
10-count carton (blister) 10-count immediate container (blister)	N/A	January 9, 2017, replaces March 31, 2106
35-count carton (bottle) 35-count immediate container (bottle)	N/A	January 9, 2017, replaces March 31, 2106
45-count carton (bottle), *Bonus 35 + 10* 45-count immediate container (bottle), *Bonus 35 + 10*	N/A	January 9, 2017, replaces March 31, 2106
55-count carton (bottle) 55-count immediate container (bottle)	N/A	January 9, 2017, replaces March 31, 2106
80-count carton (bottle) 80-count immediate container (bottle)	N/A	January 9, 2017, replaces March 31, 2106
110-count club pack / backer card (55-count X2)	N/A	January 9, 2017, replaces March 31, 2106
Bottle seal	N/A	March 31, 2016

II. REVIEWER'S COMMENTS

A. 10-count carton

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The statement "Original Prescription Strength" appears above the proprietary name.

Comment: **The following has been communicated by the Cross-Disciplinary Team Lead (CDTL) review on January 9, 2017:** ***For clarity, the "Original Prescription Strength" tag is permitted in the sponsor's case since no other strength of tablet or dosing regimen is available (for the current Xyzal levocetirizine Rx product) for the proposed OTC indications of SAR or PAR. If the sponsor submits a sNDA for Rx Xyzal that adds a population, an indication, a new tablet strength or new dosing regimen, the "Original Prescription Strength" statement would need to be reconsidered.*** **Under the conditions stated above, this is acceptable for all labels at this time.**

b. The statement of identity and pharmaceutical category, "levocertirizine dihydrochloride tablet 5mg/antihistamine" has been revised to bold face font.

Comment: **This is acceptable per §201.61(c).**

c. The NDC number placeholder has been replaced with the product NDC code.

Comment: **This is acceptable per §207.35 (b)(3).**

d. "Switzerland" is listed as the County of Origin, directly below distributor information on lower right side panel.

Comment: **After discussions with the sponsor, it has been determined that the country of origin for the active pharmaceutical ingredient (API) is Switzerland. This is acceptable.**

e. The statement [redacted] (b) (4) on the right panel has been replaced by "Clinically proven relief for 24 hours" per agency request.

Comment: **This is acceptable.**

f. The ten "X" placeholders near the recycle symbol on the bottom of the right panel have been replaced with numbers and have been identified by the sponsor as a stock number.

Comment: This is acceptable.

g. Below the Drug Facts label on back panel appears the statement, "Read directions and warnings before use. Keep this carton. It has important information."

Comment: This was recommended by the agency and is acceptable.

ii. Outer Carton Drug Facts Label

The Drug Facts label (DFL) on each label submitted has identical content regardless of count size. The updates for each section include the following:

a. *Directions*

Dosing directions have been updated [redacted] (b) (4) to be consistent with prescription labeling.

Comment: This is a recommendation made by the agency and is acceptable.

b. *Inactive ingredients*

"Polyethylene glycol" has been updated to "polyethylene glycol 400" per agency recommendation.

Comment: The inactive ingredients remain in the same order. This is acceptable.

c. *Questions or comments?*

The placeholder Xs for the toll free number have been replaced by "call 1-800-630-1610".

Comment: This is acceptable per 21 CFR §201.66(c)(9) .

d. Other sections/Issues

For all carton sizes, the Drug Facts label specifications comply with 21CFR 201.66(d).

B. 35-, 45-, 55- and 80-count cartons

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. For all cartons, the statement "Original Prescription Strength" appears above the proprietary name.

Comment: This is acceptable. See section II.A.i.a. for details.

b. The statement of identity and pharmaceutical category, "levocertirizine dihydrochloride tablet 5mg/antihistamine" have been revised to bold face font.

Comment: This is acceptable. See section II.A.i.b. for details.

c. The NDC number placeholder has been replaced with the product NDC code.

Comment: This is acceptable. See section II.A.i.c. for details.

d. For the 45-count *Bonus* carton, [redacted] (b) (4) underneath have been removed. This has been replaced with an "X" over the number "35" to the left of "45 tablets" in bold font within the orange flag indicating the net quantity of the carton.

Comment: This is acceptable per division policy on bonus labeling.

e. "Switzerland" is listed as the County of Origin, directly below distributor information on lower left side panel.

Comment: This is acceptable. See section II.A.i.d. for details.

f. The statement "Clinically proven relief from indoor and outdoor allergies" that appeared on the right side panel has been removed and replaced by "Clinically proven relief for 24 hours".

Comment: This is acceptable.

g. The interior left- panel of all cartons removed the following:

[redacted] (b) (4)

And replaced with "Clinically Proven 24 hour Relief of Indoor and Outdoor Allergies" in bold blue font.

Comment: This is acceptable.

h. The ten "X" placeholders near the recycle symbol on the bottom of the left panel have been replaced with numbers and have been identified by the sponsor as a stock number.

Comment: This is acceptable.

i. Below the Drug Facts label on the left panel appears the statement, "Read directions and warnings before use. Keep this carton. It has important information."

Comment: This is acceptable. See section II.A.i.g. for details.

ii. Outer Carton Drug Facts Label

The Drug Facts label (DFL) on each label has identical content regardless of count size. The updated sections include the following:

a. ***Directions***

Dosing directions have been updated (b) (4) to be consistent with prescription labeling.

Comment: This is acceptable. See section II.A.ii.a. for details.

b. ***Inactive ingredients***

"Polyethylene glycol" has been updated to "polyethylene glycol 400" per agency recommendation.

Comment: This is acceptable. See section II.A.ii.b. for details.

c. ***Questions or comments?***

The placeholder Xs for the toll free number have been replaced by "call 1-800-630-1610".

Comment: This is acceptable. See section II.A.ii.c. for details.

C. 110-count club pack carton

i. Outer Carton outside Drug Facts Label

Principal Display Panel

a. The statement "Original Prescription Strength" appears above the proprietary name.

Comment: This is acceptable. See section II.A.i.a. for details.

b. The statement of identity and pharmaceutical category, "levocertirizine dihydrochloride tablet 5mg/antihistamine" has been revised to bold face font.

Comment: This is acceptable. See section II.A.i.b. for details.

c. The NDC number placeholder has been replaced with the product NDC code in upper left corner.

Comment: This is acceptable. See section II.A.i.c. for details.

d. Stock number has been added to bottom right corner of PDP.

Comment: Although this is an addition to the March 31, 2016 label, it is not considered a labeling issue and does not interfere with the PDP. This is acceptable.

Back Panel

e. The statement "Clinically proven relief from indoor and outdoor allergies" on the right side of back panel has changed to "Clinically Proven Relief For 24 Hours"

Comment: This is acceptable. See section II.A.i.e. for details.

f. "Switzerland" is listed as the County of Origin, directly below distributor information.

Comment: This is acceptable. See section II.A.i.d. for details.

g. The ten "X" placeholders near the recycle symbol on the bottom of the right panel have been moved to the bottom left and replaced with numbers and have been identified by the sponsor as a stock number.

Comment: This is acceptable.

i. Below the Drug Facts label appears the statement, "Read directions and warnings before use. Keep this carton. It has important information."

Comment: This is acceptable. See section II.A.i.g. for details.

ii. Outer Carton Drug Facts Label

The Drug Facts label (DFL) on each label has identical content regardless of count size. The DFL is displayed on the back panel of club card. Updates are as follows:

a. ***Directions***

Dosing directions have been updated (b) (4) to be consistent with prescription labeling.

Comment: This is acceptable. See section II.A.ii.a. for details.

b. ***Inactive ingredients***

"Polyethylene glycol" has been updated to "polyethylene glycol 400" per agency recommendation.

Comment: This is acceptable. See section II.A.ii.b. for details.

c. ***Questions or comments?***

The placeholder Xs for the toll free number have been replaced by "call 1-800-630-1610".

Comment: This is acceptable. See section II.A.ii.c. for details.

D. 10-count (blister) immediate container, 35-, 45-, 55-and 80-count (bottle) immediate containers.

a. 10-count (blister) immediate container

The immediate container has been updated with the stock number replacing the placeholder Xs in the center panel.

Comment: This is acceptable.

b. 35-, 45-, 55-and 80-count (bottle) immediate containers.

i. The statement "Original Prescription Strength" appears above the proprietary name.

Comment: This is acceptable. See II.A.i.a. for details.

ii. The statement of identity and pharmaceutical category, "levocertirizine dihydrochloride tablet 5mg/antihistamine" has been revised to bold face font.

Comment: Although not required for an immediate container that is not viewed by the consumer at point of purchase, this is acceptable. See II.A.i.b. for details.

iii. The NDC number placeholder on the upper right of the PDP and on the base panel has been replaced with a product NDC code.

Comment: This is acceptable. See section II.A.i.c. for details.

iv. The ten placeholder Xs placed above the distributor information have been replaced with a stock number.

Comment: This is acceptable. See section II.A.ii.f. for details.

v. "Switzerland" is listed as the County of Origin, directly below distributor information.

Comment: This is acceptable. See section II.A.i.d. for details.

vi. In the unformatted Drug Facts, the following has been updated:

- Dosing directions have been updated (b) (4) to be consistent with prescription labeling.
- "Polyethylene glycol" has been updated to "polyethylene glycol 400" per agency recommendation.
- The placeholder Xs for the toll free number have been replaced by "call 1-800-630-1610".

Comment: These are all acceptable. See sections I.A.ii.a-c for details.

III. RECOMMENDATIONS

Issue an APPROVAL letter to the sponsor for the submitted Xyzal Allergy 24HR tablet labeling and request final printed labeling. The final printed labeling (FPL) must be identical to the labeling submitted on January 9, 2017 as follows:

- 10-count carton (blister)
- 10-count immediate container (blister)
- 35-count carton (bottle)
- 35-count immediate container (bottle)

- 45-count *Bonus* carton (bottle)
- 45-count *Bonus* immediate container (bottle)
- 55-count carton (bottle)
- 55-count immediate container (bottle)
- 80-count carton (bottle)
- 80-count immediate container (bottle)
- 110-count Club Pack (bottle)

Submit FPL identical to labels submitted on March 31, 2016

- Bottle seal

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

12 Page(s) of Draft Labeling 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/

KAREN E LIVORNESE
01/20/2017

KEVIN L LORICK
01/23/2017
I concur with the review and recommendation

FDA Social Science Review:
Label Comprehension Study

Division of Nonprescription Drug Development

Date:	December 19, 2016
From:	Amanda Pike-McCrudden, MAA, Social Scientist, DNDP
Through:	Steven Osborne, MD, Clinical Team Leader, DNDP
To:	Theresa Michele, MD, Director, DNDP
Subject:	Label Comprehension Study supporting the over-the-counter (OTC) approval of Xyzal (levocetirizine dihydrochloride 5mg), an antihistamine indicated for the temporary relief of symptoms due to hay fever or other respiratory allergies (runny nose, sneezing, itchy, watery eyes and itching of the nose or throat) in adults and children ages 6 and older.

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1. Executive Summary

The Sponsor conducted a label comprehension study supporting the over-the-counter (OTC) approval of Xyzal (levocetirizine dihydrochloride 5mg), an antihistamine indicated for the temporary relief of symptoms due to hay fever or other respiratory allergies (runny nose, sneezing, itchy, watery eyes and itching of the nose or throat) in adults and children ages 6 and older.

The label comprehension study was fielded without prior review of the protocol and included testing on three warnings from the label pertaining to kidney disease and urinary retention in 417 consumers ages 16 years and older. No label testing was conducted on understanding of somnolence.

Overall, there was consumer comprehension on the warnings although there was some confusion on proper course of action and the difference between the bladder and kidneys. Ultimately, consumers chose a safe or more conservative course of action in response to the scenario questions posed to them in the study.

2. Background

Levocetirizine dihydrochloride is an oral histamine H1 receptor antagonist and the active R-enantiomer of the approved racemate, cetirizine. It is solely responsible for the antihistaminic activity of cetirizine. Levocetirizine dihydrochloride tablets were originally approved for prescription use in 2007 under NDA 22-064 for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children 6 years of age or older, and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 years of age and older. Subsequently, the indication for the relief of symptoms associated with SAR was extended to children 2 years of age and older and for the relief of PAR and the treatment of CIU for children 6 months of age and older in a supplemental NDA (S017) on August 21, 2009 to address the Pediatric Research Equity Act (PREA) requirement.

The CIU indication is not being switched to nonprescription use at this time as agreed to with the Division of Nonprescription Drug Products (DNDP) in the Sanofi-Agency conference call on December 22, 2015.

A Label Comprehension Study was conducted in support of this switch. There was no Social Science review of the study protocol before fielding.

The proposed nonprescription use of levocetirizine dihydrochloride is for the temporary relief of symptoms due to hay fever or other respiratory allergies (runny nose, sneezing, itchy, watery eyes and itching of the nose or throat).

3. Label Comprehension Study

Design and Conduct

This was a multi-site, single-visit, pivotal label comprehension study in consumers ages 16 years and older. The purpose of the study was to evaluate subjects' comprehension of specific warnings and directions related to kidney disease and urinary retention on the proposed Xyzal OTC label.

This study was completed with 417 unique subjects ages 16 years and older with 27.8% of the study population testing as low literate. Eight (8) geographically dispersed research sites in the United States were used to recruit and interview subjects.

Qualified subjects were invited to the research site for the study. For literacy testing, adult subjects 18 years of age and older completed the Rapid Estimate of Adult Literacy in Medicine (REALM), and adolescent subjects 16-17 years of age completed the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) test. Subjects were then presented with the product carton for the proposed Xyzal Allergy 24HR product and given the opportunity to review the package labeling at their own pace.

Once the subject indicated they had finished reviewing the DFL, the pivotal label comprehension interview was conducted. The product labeling remained in full view of and accessible to the subject during the assessment. The label comprehension questionnaire was comprised of scenario-based or direct open-ended questions that required the consumer to make decisions about the situation based on the information on the DFL. All open-ended questions will be followed by a probe (why do you say that) in order to obtain the subject's rationale for the response; these responses will be captured verbatim.

Once a subject moved on to the next question, they were not permitted to change answers to any previous questions. The subject's comprehension response and follow-up verbatim comment were recorded and used in coding the responses as correct or incorrect as part of the data analysis. The comprehension questions were presented in a mixed order and not in the order that the communication objectives appear on the label.

Details of the study population:

Potential subjects were recruited by 8 geographically dispersed market research sites from their respective databases. Screeners used the following inclusion and exclusion criteria to determine eligible participants:

Inclusion Criteria

The following inclusion criteria will be applied to all participants:

1. The subject is 16 years of age or older.
2. The subject is able to speak, read and understand English sufficiently to understand the nature of the study procedures.
3. The subject must be willing, able and likely to comply with all study procedures.
4. At the study site, the subject must read and voluntarily sign the Confidentiality/Non-Disclosure Agreement (CDA) and Agreement to Participate ATP.

Exclusion Criteria

The following exclusion criteria will be applied to all participants:

1. The subject has ever been trained or employed as a healthcare professional.
2. The subject or anyone in their household is currently employed by any of the following:
    a. A marketing or marketing research company
    b. An advertising agency or public relations firm
    c. A pharmacy or pharmaceutical company
    d. A manufacturer of medicines
    e. A managed care or health insurance company as a healthcare professional
3. The subject has, or cannot remember if he/she has, participated in any market research study, product label study or clinical trial in the past twelve (12) months.
4. The subject normally wears corrective lenses, contacts or glasses to read and does not have them with him/her.
5. The subject has any impairment that would prevent him/her from being able to read on his/her own.

Demographics of the study population are detailed in table 9-1 below:

Table 9-1 Demographics: General Population

Demographics	Total		Normal Literacy		Low Literacy	
Total Responding	**417**		**301**		**116**	
	n	**%**	**n**	**%**	**n**	**%**
Gender						
Male	176	42.2	129	42.9	47	40.5
Female	241	57.8	172	57.1	69	59.5
Age						
16 to 17	20	4.8	14	4.7	6	5.2
18 to 24	47	11.3	33	11.0	14	12.1
25 to 34	56	13.4	42	14.0	14	12.1
35 to 44	68	16.3	49	16.3	19	16.4
45 to 54	87	20.9	64	21.3	23	19.8
55 to 64	75	18.0	56	18.6	19	16.4
65 or older	64	15.3	43	14.3	21	18.1
Race						
Caucasian/White	247	59.2	198	65.8	49	42.2
African American/Black	86	20.6	42	14.0	44	37.9
Native American	1	0.2	1	0.3	0	--
Asian or Pacific Islander	11	2.6	9	3.0	2	1.7
Other	72	17.3	51	16.9	21	18.1
Hispanic Origin						
Yes	71	17.0	52	17.3	19	16.4
No	346	83.0	249	82.7	97	83.6
Education (16-17)						
9th Grade	1 (20)	5.0	0 (14)	--	1 (6)	16.7
10th Grade	6 (20)	30.0	4 (14)	28.6	2 (6)	33.3
11th Grade	10 (20)	50.0	7 (14)	50.0	3 (6)	50.0
12th Grade	3 (20)	15.0	3 (14)	21.4	0 (6)	--
Education (18+)						
Less than high school	35 (397)	8.8	12 (287)	4.2	23 (110)	20.9
Completed high school/ GED	94 (397)	23.7	57 (287)	19.9	37 (110)	33.6
Some College/ Technical School	131 (397)	33.0	104 (287)	36.2	27 (110)	24.5
Graduated College/ Technical School or more	136 (397)	34.3	113 (287)	39.4	23 (110)	20.9
Refused	1 (397)	0.3	1 (287)	0.3	0 (110)	--

Table 9-1 Demographics: General Population

Demographics	Total		Normal Literacy		Low Literacy	
Total Responding	**417**		**301**		**116**	
	n	**%**	**n**	**%**	**n**	**%**
Income						
$0 to $14,999	54	12.9	22	7.3	32	27.6
$15,000 to $24,999	45	10.8	29	9.6	16	13.8
$25,000 to $34,999	41	9.8	26	8.6	15	12.9
$35,000 to $44,999	51	12.2	39	13.0	12	10.3
$45,000 to $64,999	71	17.0	56	18.6	15	12.9
$65,000 to $74,999	34	8.2	24	8.0	10	8.6
$75,000 or more	116	27.8	101	33.6	15	12.9
Refused	5	1.2	4	1.3	1	0.9
Employment Status						
Employed full-time	161	38.6	131	43.5	30	25.9
Employed part-time	85	20.4	64	21.3	21	18.1
Unemployed	47	11.3	24	8.0	23	19.8
Student	39	9.4	24	8.0	15	12.9
Retired	66	15.8	45	15.0	21	18.1
Homemaker	8	1.9	5	1.7	3	2.6
Disabled	8	1.9	5	1.7	3	2.6
Self-employed	2	0.5	2	0.7	0	--
Other	1	0.2	1	0.3	0	--
REALM Category						
Low Literacy	116	27.8	0	--	116	100.0
Normal Literacy	301	72.2	301	100.0	0	--

Source: Tabulated Data

Primary Objective:
The primary objective of this study was to evaluate the ability of consumers to comprehend 3 specific warnings and directions on the Xyzal Allergy 24HR DFL related to kidney disease and urinary retention:
1) Do not use if you have kidney disease
2) Ask a doctor before use if you have ever had trouble urinating or emptying your bladder
3) Stop use and ask a doctor if you have trouble urinating or emptying your bladder

The success threshold for each primary objective was that the lower bound of a two-sided 95% confidence interval of the comprehension rate was at least 85%.

Secondary Objective:
The secondary objective of this study was to understand reasons for consumer confusion about the direction to "ask a doctor before use if you have ever had trouble urinating or emptying your bladder".
No success thresholds were set for the secondary objective.

The following warnings, which are consistent with other OTC antihistamine medications, were not tested because they can be found on other approved OTC labeling. Communication objectives that will not be tested (i.e. on other approved OTC labeling):

1. Do not use
    a. If you have ever had an allergic reaction to this product or to any of its ingredients or to an antihistamine containing cetirizine
2. When using this product
    a. Drowsiness may occur
    b. Avoid alcoholic drinks
    c. Alcohol, sedatives, and tranquilizers may increase drowsiness
    d. Be careful when driving a motor vehicle or operating machinery
3. Stop use and ask a doctor if
    a. An allergic reaction to this product occurs. Seek medical help right away.
4. If pregnant or breast-feeding
    a. If breast-feeding: not recommended
    b. If pregnant: ask a health professional before use
5. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222)

Table 10-1 Primary Communication Objectives With Corresponding Scenarios and Follow-up Questions

Primary Communication Objective	Scenario and Question(s)
Ask a doctor before use if you have ever had trouble urinating or emptying your bladder	**Scenario:** • *Last month, Alex was having trouble emptying his bladder when he went to the bathroom.* • *He also suffers from allergies and now he wants to start using this product.* **Q2a:** According to the label, what, if anything, should Alex do? **Q2b:** Why do you say that?
Do not use if you have kidney disease	**Scenario:** • *Sally has kidney disease.* • *She would like to start using this product to treat her allergies.* **Q4a:** According to the label, is it okay or not okay for Sally to use this product? **Q4b:** Why do you say that?
Stop use and ask a doctor if you have trouble urinating or emptying your bladder	**Scenario:** • *Erin has been taking this product for several days.* • *She is now having trouble urinating and has never had this problem before.* **Q5a:** According to the label, what, if anything, should Erin do? **Q5b:** Why do you say that?

Source: Label Comprehension Questionnaire

Analysis:

Responses were analyzed in a two-step process, where the responses to the initial question were evaluated as correct or incorrect and then the follow-up probe was evaluated as correct or incorrect. The correct/incorrect determinations to both the initial and follow-up questions were then examined together to determine whether the overall response was correct or incorrect. Answers were coded and analyzed according to the following rubric:

Initial/Follow-Up Net Code	Final Code
Correct Initially, Correct at Follow-Up	Correct Overall Response
Correct Initially, Acceptable at Follow-Up	Correct Overall Response
Correct Initially, Incorrect at Follow-Up	Incorrect Overall Response
Acceptable Initially, Correct at Follow-Up	Correct Overall Response
Acceptable Initially, Acceptable at Follow-Up	Correct Overall Response
Acceptable Initially, Incorrect at Follow-Up	Incorrect Overall Response
Incorrect Initially, Correct at Follow-Up	Correct Overall Response
Incorrect Initially, Acceptable at Follow-Up	Correct Overall Response
Incorrect Initially, Incorrect at Follow-Up	Incorrect Overall Response

Coding principles indicated when the answer to an open-ended question was considered acceptable and provided the rationale for that net code.

Correct Initially, Correct at Follow-Up

Subject provided a correct response at the initial question (Q.A) and, upon consideration of the follow-up question (Q.B), demonstrated an understanding of the objective.

Correct Initially, Acceptable at Follow-Up

Subject provided a correct response at the initial question (Q.A) and upon consideration of the follow-up question (Q.B), did not discredit his/her initial response, but did not verbalize both aspects of the correct response.

Correct Initially, Incorrect at Follow-Up

Subject provided a correct response at the initial question (Q.A) and, upon consideration of the follow-up question (Q.B), did not demonstrate an understanding of the objective.

Acceptable Initially, Correct At Follow-Up

Subject demonstrated an understanding of the primary aspect of the objective at the initial question (Q.A) and, upon consideration of the follow-up question (Q.B), demonstrated an understanding of the objective.

Acceptable Initially, Acceptable At Follow-Up

Subject demonstrated an understanding of the primary aspect of the objective at the initial question (Q.A) and, upon consideration of the follow-up question (Q.B), did not discredit his/her initial response, but did not verbalize both aspects of the correct follow-up response.

Primary Analysis:

The primary analysis was performed by dividing the number of subjects with an overall correct response by the total number of responses to the question. The lower bound of a two-sided 95% confidence limit was computed using the Clopper-Pearson method; success was determined according to the pre-specified threshold of 85%.

Table 10-2 Primary Objectives: Overall Correct Responses Demonstrating Comprehension

(Question #) Objective	Total Study Population N=417		
	n	PE%	95% CI
(Q.5) **Stop Use and Ask a Doctor if** You have trouble urinating or emptying your bladder	406	97.4	95.3, 98.7
(Q.4) **Do Not Use** If you have kidney disease	384	92.1	89.1, 94.5
(Q.2) **Ask a Doctor before Use if You Have** ever had trouble urinating or emptying your bladder	276	66.2	61.4, 70.7

Source: Tabulated Data

The success threshold was met for the overall study population on questions 5 and 4 with lower-bounds of 95.3% and 89.1%, respectively. The success threshold was not initially met for question 2 (61.4%) regarding the warning to ask a doctor before use if you have ever had trouble urinating or emptying your bladder.

Secondary Analysis and Mitigation:

The secondary objective for this study was to ascertain reasons for consumer confusion on question number 2, the lowest scoring objective. For this analysis, verbatim responses were reviewed and analyzed. For question 2, the majority of incorrect responses prior to mitigation (n=94 of 141) indicated either a more conservative, or a safe course of action: "Do not use the product" (n=66) or "Ask a doctor" without a fully correct rationale (n=28). These responses were anticipated *a priori* by the sponsor and were planned as mitigations, based on results from iterative qualitative testing. This does suggest that consumers recognized the potential risk and gave an answer incorporating a safe course of action. After mitigating the 94 responses, the overall correct comprehension score improved from 66.2% to 88.7% [n=370; 95% CI: (85.3%, 91.6%)].

According to the responses, there does appear to be some consumer confusion between the bladder and kidneys. There are also two warnings on the label pertaining to the bladder; one with a "stop use" warning while the other is the "ask a doctor before use" warning. Additionally, there were 22 responses coded as incorrect for referencing the "stop use" bladder warning instead of the "ask a doctor" bladder warning on the initial response to the question. Those 22 responses were not mitigated.

Subgroup Analysis: Literacy and Age

Table 10-3 Analysis of Primary Objectives: Normal vs Low Literacy

(Question #) Objective	Normal Literacy N=301			Low Literacy N=116		
	n	PE%	95% CI	n	PE%	95% CI
(Q.5) **Stop Use and Ask a Doctor if** You have trouble urinating or emptying your bladder	293	97.3	94.8, 98.9	113	97.4	92.6, 99.5
(Q.4) **Do Not Use** If you have kidney disease	286	95.0	91.9, 97.2	98	84.5	76.6, 90.5
(Q.2) **Ask a Doctor before Use if You Have** ever had trouble urinating or emptying your bladder	204	67.8	62.2, 73.0	72	62.1	52.6, 70.9

Source: Tabulated Data

Overall, results for the low literacy subgroup were within approximately ten percentage points of the normal literacy subgroup for all three objectives' composite scores. The low literacy comprehension score for the objective 'Stop use and ask a doctor if you have trouble urinating or emptying your bladder' was nearly equivalent to the normal literacy subgroup score.

One area of concern is the lower bound of 76.6% in the low literacy population for question 4 regarding the 'do not use' kidney warning. Of note, among all incorrect responders (normal and low literacy), most referenced "Asking a Doctor before Use", indicating that a subject with kidney disease would understand not to use the product, or would ask their doctor before using the product. This does show understanding of a warning regarding kidney disease with an incorrect action ('ask a doctor before use' instead of 'do not use'). It is possible that this is another example of confusion between the kidney and bladder (referencing the bladder warning as rationale for the kidney disease response). This should be taken into consideration by the sponsor to determine if any additional steps could be taken to highlight the kidney warning on the label. It is also worth noting that the warning statement was not tested, to our knowledge, in a population of consumers with kidney disease. It is always possible that consumers who have kidney disease would take greater notice of that warning than the general population.

Both literacy subgroups scored below 70% prior to mitigation for the objective 'Ask a doctor before use if you have ever had trouble urinating or emptying your bladder'. When including mitigated responses, scores improved to 90.0% (271/301) for normal literacy and 85.3% (99/116) for Low Literacy.

Table 10-4 Analysis of Primary Objectives: Teen Subjects vs. Adults Subjects

(Question #)	Objective	Teen Subjects N=20			Adults Subjects N=397		
		n	PE%	95% CI	n	PE%	95% CI
(Q5)	**Stop Use and Ask a Doctor if** You have trouble urinating or emptying your bladder	20	100.0	83.2, 100.0	386	97.2	95.1, 98.6
(Q4)	**Do Not Use** If you have kidney disease	18	90.0	68.3, 98.8	366	92.2	89.1, 94.6
(Q2)	**Ask a Doctor before Use if You Have** ever had trouble urinating or emptying your bladder	8	40.0	19.1, 64.0	268	67.5	62.7, 72.1

Source: Tabulated Data

Teen scores were similar to adult scores for two of the three objectives. Teens scored lower than adults for the 'Ask a doctor before use if you have ever had trouble urinating or emptying your bladder' both prior to and after mitigation. It is worth noting that of the 7 teen responses classified as incorrect after mitigation, 2 of them could possibly be interpreted as correct for referencing the 'stop use' instead of 'before use' bladder warning. Overall, the teen population of 20 respondents is too small to draw generalizable conclusions from the data and so I am not concerned that comprehension differed in a statistically significant way on Question 2.

4. Conclusions and Recommendations

Overall, consumers ages 16 years and older demonstrated comprehension of the risks and warnings relating to kidney disease and urinary retention on the proposed Xyzal Allergy 24HR label. The primary endpoints were met or mitigated demonstrating that consumers understood the warnings or understood potential risks and responded with a more conservative response or a safe course of action.

One recommendation to the sponsor would be to further highlight in some way the kidney disease warning, ensuring that it is both easy to find and easy to distinguish from the two bladder warnings in terms of determining the proper course of action.

5. Appendix

APPEARS THIS WAY ON ORIGINAL

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

/s/

AMANDA H PIKE-MCCRUDDEN
12/22/2016

STEVEN F OSBORNE
12/22/2016

Labeling Review for
Children's Xyzal® Allergy 24HR
Draft Labeling

SUBMISSION DATES:	March 31, 2016
NDA/SUBMISSION TYPE:	209090 (Rx-to-OTC switch)
ACTIVE INGREDIENTS:	Levocetirizine dihydrochloride 2.5 mg / 5 mL
DOSAGE FORM	Oral Solution
SPONSOR:	Sanofi US Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 Cynthia Psaras, PhD, Director, Global Regulatory Affairs 908-981-4874
REVIEWER:	Karen Livornese, RN, MSN, DNDP/ODE IV
TEAM LEADER:	Steven Adah, Ph.D., DNDP/ODE IV
ASSOCIATE DIRECTOR for LABELING	Ruth E. Scroggs, PharmD, DNDP/ODE IV
REGULATORY PROJECT MANAGER	Sherry Stewart, Project Manager, DNDP/ ODE IV

I. BACKGROUND

UCB, Inc. and its agent, Sanofi US Services, Inc., submitted on March 31, 2016, as an original new drug application (NDA) 209090, under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act). The sponsor proposes a partial-switch from NDA 22-157 to market an oral solution form of the antihistamine levocetirizine dihydrochloride 2.5 mg / 5 mL as an over-the-counter (OTC) product for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in children and adults 2 years of age and older. The chronic idiopathic urticarial (CIU) indication is not being switched to nonprescription use at this time. The approved prescription for of Children's Xyzal ® (levocetirizine dihydrochloride) 2.5 mg / 5 mL oral solution, NDA 22-157, is used as the reference listed drug (RLD). The oral solution form of certirizine hydrochloride 1 mg / mL is currently approved as an OTC product in NDA 22-155 (Children's Zyretc® Allergy), and is also referenced in this application.

This is a review of the labeling submitted March 31, 2016 and is the initial review for this application.

Submitted Labeling	Representative of Following SKUs	Date Submitted
5 fluid ounce (fl oz) carton (bottle), *Children's Tutti-Frutti Flavor* 5 fluid ounce (fl oz) immediate container (bottle)		March 31, 2016
Oral Solution Dosing Cup representation	N/A	March 31, 2016
Bottle seal	N/A	March 31, 2016

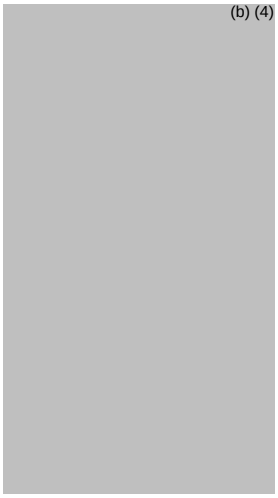
II. REVIEWER'S COMMENTS

A. 5 fluid ounce (fl oz) carton

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The background of the principal display panel (PDP) is multicolored with a centered, concentric circular pattern. From the top of the PDP down, the colors are dark blue, light blue, white, yellow, light orange and then orange on the bottom. This pattern continues on both side panels. The back panel's background is dark blue. The proposed proprietary name, "Children's XYZAL®ALLERGY 24HR" is in bold font with "Children's" in light blue, "Xyzal Allergy" in dark blue and "24HR" is in orange font. There is a light blue and dark blue semi-circle above the proprietary name and an orange and yellow semi-circle below it. See below:



Comment: **The proposed proprietary name is acceptable per DMEPA's letter of May 26, 2016. DMEPA has concluded in their review, dated December 16, 2016, that the label container and carton designs are acceptable from a medication error perspective. DMEPA makes the recommendation for a graphic of the dosing cup (empty) on PDP and side panel with lined measurements visible.**

b. The statement of identity and pharmaceutical category, "levocetirizine dihydrochloride oral solution 2.5 mg / 5 ml antihistamine" appears below the proprietary name in dark-blue, non-bolded font.

Comment: **This is not acceptable. In accordance with §201.61(c), the statement of identity shall be presented in bold face type on principal display panel. In addition, the acceptable abbreviation for milliliter is "mL", not "ml".**

c. The NDC number appears on the upper left corner of the PDP represented with placeholder Xs.

Comment: **This is not acceptable. Replace the placeholder Xs with the actual NDC number in accordance with §207.35 (b)(3).**

d. In the upper right corner of PDP, there is a light blue circular graphic with "2+" in bold white font inside. The statement "Ages 2 Years & Older" are in light blue font to the left of the circular graphic.

Comment: **Approved labeling for NDA 22-157 includes dosing guidelines for children 6 months to adults. DNDP clinical team has reviewed this and deems 2 years and older to be acceptable.**

e. On the lower section of the PDP, the statement "24 hour Relief of" in bold blue font sits directly above four bulleted symptoms in bold blue font that reads as follows:

- Sneezing

- Runny Nose
- Itchy Nose or Throat
- Itchy, Watery Eyes

Comment: This is a true statement in the "Uses" section of the Drug Facts label and is acceptable.

f. The declaration of net quantity of contents, "5 fl.oz. (148 ml)" appears in white, non-bolded font on an orange flag on the lower right side of the carton.

Comment: This is not acceptable. The net quantity shall be in boldface font accordance with §201.62 (g). Also, the abbreviation for milliliter is incorrect; see section II.A.i.b. for details.

g. A graphic of a peach with two green leaves on the top, an orange half and two cherries with one green leaf at the top of the stems, are on the lower left corner of PDP.

Comment: DMEPA has reviewed carton design without objection of this graphic. Therefore, this is acceptable.

h. The statement "Tutti Frutti Flavor" is in yellow font in lower right corner of PDP.

Comment: Per CMC review correspondence dated on November 29, 2016, there is no change in formulation with NDA 22-157. This is acceptable.

Left Panel Background

i. See II.A.i.a. for details.

Comment: This is acceptable.

j. The statement "Dye Free - Alcohol Free" is at the top of the left panel in bold (b) (4) font.

Comment: CMC has confirmed this statement is accurate in correspondence dated November 29, 2016. This is acceptable.

k. The statement "Clinically proven relief from indoor and outdoor allergies" appears on the upper section of the left side panel on a blue, elongated hexagon with orange outline on left and blue outline on right with bold white font.

Comment: Per correspondence from DPARP on November 29, 2016, this statement is not misleading and therefore is acceptable.

l. In the center of the left panel the proposed proprietary name, "Children's XYZAL®ALLERGY 24HR" is in bold font with "Children's in light blue, "Xyzal Allergy" in dark blue and "24HR" is in orange font. There is a light blue and dark blue semi-circle above the proprietary name and an orange and yellow semi-circle below it.

Comment: This is acceptable. See section II.A.ii.a for details.

m. The statement (b) (4) (b) (4)

Comment: This is not acceptable. DPARP review confirms that duration of effect of at least 24 hours. The recommendation is to comply with drug class labeling, "24 hour relief".

n. On the lower section of the left panel the statements, "Use Only With Enclosed Dosing Cup" and "Wash and let air dry after each use" are in white font.

Comment: DMEPA has reviewed carton design without objection of these statements. Therefore, this is acceptable.

o. The bottom of the back panel contains the Trademark, Distributer and Copyright information in white font. See below:

> "The trade dress of this Xyzal® package is
> subject to trademark protection.
> Dist By: Chattem, Inc., a Sanofi Company, Chattanooga, TN 37409-219
> ©2017"

Comment: This complies with §201.61 and is acceptable.

p. "Canada" is listed as the County of Origin, directly below distributor information on lower right side panel.

Comment: This is not acceptable. Through CMC review, the countries that manufacture the API are Switzerland (b) (4)

q. On the bottom right corner of back panel is a series of X place holders and a circular, three arrow recycling graphic in (b) (4) font.

Comment: This is not considered labeling. Request sponsor for explanation.

r. Top panel has the proprietary name, "Children's Xyzal® Allergy 24 HR" with "Children's " in light blue bold font in a semi-circular arc and "Xyzal® Allergy 24 HR" in bold white font.

Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

The Drug Fact label (DFL) is listed on the right side panel and continues to the back panel.

a. ***Active ingredient (in each 5mL): "Levocetirizine dihydrochloride 2.5 mg"***

Comment: This is identical to the Xyzal oral solution DFL (RLD) and is acceptable.

b. ***Purpose: "Antihistamine"***

Comment: This is acceptable as required under 21 CFR 201.66(c)(3).

c. ***Uses: "temporarily relieves these symptoms due to hay fever or other respiratory allergies:***

- **runny nose**
- **sneezing**
- **itchy, watery eyes**
- **itching of the nose or throat"**

Comment: This complies with labeling in NDA 22-155 (Children's Zyrtec® Allergy) and is with *Labeling of antihistamine drug products* per §341.72(b)(1). Therefore, this is acceptable.

d. ***Warnings***

1. "Do not use

- if you have kidney disease
- if you have ever had an allergic reaction to this product or any of its ingredients or to an antihistamine containing certirizine"

Comment: DNDP clinical team does not disagree with these statements. These are acceptable.

2. "Ask a doctor before use if you have

- ever had trouble urinating or emptying your bladder"

Comment: DNDP clinical team does not disagree with this statement. This is acceptable.

3. "When using this product:
- drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery"

Comment: This reflects the statements in the RLD and is acceptable.

4. "Stop use and ask a doctor if
- you have trouble urinating or emptying your bladder
- an allergic reactions to this product occurs. Seek medical help right away."

Comment: This reflects the statements in the RLD and is acceptable.

5. "If pregnant or breast-feeding:
- if breast-feeding: not recommended
- if pregnant: as a health professional before use"

Comment: This statement complies with 21CFR 201.63(a) and 201.66(c)(5)(ix), and therefore is acceptable.

6. "Keep out of reach of children".
"In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222)." There is an arrow at the bottom of this statement pointing to the adjacent panel with the continued DFL.

Comment: This statement complies with 21CFR 330.1(g) and 201.66(c)(5)(x), and therefore is acceptable.

e. ***Directions***

[Bullet] "use only with enclosed dosing cup"
This section is in a two column table format with six rows for dosing directions:
Row 1; Column 1: "adults 65 years of age and older"
Row 1: Column 2: "[bullet] ask a doctor"
Row 2; Column 1: "adults and children 12-64 years of age"
Row 2; Column 2: (b) (4)

"[bullet] do not take more than 1 mL in 24 hours"

Row 3; Column 1: "children 6-11 years of age"

(b) (4)

Row 5; Column 1: "children under 2 years of age"
Row 5; Column 2: "[bullet] do not use"
Row 6; Column 1: "consumers with kidney disease"
Row 6; Column 2: "[bullet] do not use"
"Note: mL = milliliters

See graphic below:

(b) (4)

Comment: DNDP clinical team recommends that the directions reflect the approved labeling for NDA 22-157 to include dosing that states, "once daily in the evening". Clinical reviewer concurs with "ask a doctor" for 65 years and older. Children under 2 and renal impairment are given guidelines in the RLD. Clinical team accepts "do not use" for these two populations.

f. ***Other information***

The following bullets appear:

"[bullet] each 5 mL contains: **sodium 3.2 mg"**

"[bullet] store between 20° and 25°C (68° and 77°F)".
"[bullet] safety sealed: do not use if carton was opened or if printed foil inner seal is torn or missing."

Comment: This section contains the tamper evident statement within the DFL which is acceptable per §211.132. This section also discloses sodium content. Per CMC correspondence dated November 29, 2016, "sodium 3.2 mg" is deemed acceptable. Storage statement reflects RLD and is acceptable.

g. *Inactive ingredients*

The following is the list of inactive ingredients in alphabetical order: *flavor, glacial acetic acid, glycerin, maltitol solution, methylparaben, propylparaben, purified water, saccharin sodium, sodium acetate trihydrate"*

Comment: CMC review has confirmed acceptability of inactive ingredients. Therefore, This is acceptable.

h. *Questions or comments?*

"call 1-800-XXX-XXXX"

Comment: This is not acceptable. Replace the placeholder Xs with an actual telephone number. 21 CFR 201.66(c)(9) requires that this section contain a telephone number of a source to answer questions about the product. We also recommend that the label include the days of the week and times that the toll-free number is in operation.

i. **Other sections/Issues**

- The Drug Facts label specifications comply with 21CFR 201.66(d).

B. 5 fluid ounce (fl. oz.) immediate container (bottle)

Face Label
The background is similar to the carton label which is multicolored with a centered, concentric circular pattern. From the top of the immediate container down, the colors are dark blue, light blue, white, yellow, light orange and then orange on the bottom. This pattern continues from the front to the back. The proposed proprietary name, "Children's XYZAL®ALLERGY 24HR" is in bold font with "Children's in light blue, and "Xyzal® Allergy 24HR" is in dark blue font. There is a dark blue semi-circle above the proprietary name and an orange semi-circle below it. The back label contains the Drug Facts.
See Below:

Comment: This is acceptable. See II.A.i.a. for details.

i. The statement of identity and pharmaceutical category, "levocetirizine dihydrochloride oral solution 2.5 mg / 5 ml antihistamine" appears below the proprietary name in dark-blue, non-bolded font.

Comment: Since this is not placed on the PDP, but inside a carton at point of purchase for retail, §201.61 does not apply. However, it is recommended that SOI presented in bold font. Also, "ml" is used as measurement rather than "mL". This is not acceptable.

ii. The NDC number appears on the upper left corner of the face label represented with placeholder Xs.

Comment: This is not acceptable. See section II.A.i.c. for details.

iii. In the upper right corner of face label, the statement, "Ages 2 years & Older" in bold white font.

Comment: This is acceptable. See section II.A.i.d. for details.

iv. On the lower section of the face label, the statement "24 hour Relief of" in bold blue font is on the lower left section and directly to the right are four bulleted symptoms in bold blue font that reads as follows:

[bullet]Sneezing Itchy [bullet] Nose or Throat
[bullet] Runny Nose Itchy, [bullet] Watery Eyes

Comment: This is acceptable. See section II.A.i.e. for details.

v. In the lower left corner of the face label is the statement "Tutti Frutti Flavor" in bold dark blue font.

Comment: This is acceptable. See section II.A.i.h. for details.

vi. The declaration of net quantity of contents, "5 fl.oz. (148 ml)" appears in blue font on lower right corner of face label.

Comment: Although this is not the PDP, this is not acceptable. See section II.A.i.f for details.

The back panel of the immediate container label has the unformatted drug facts label divided into two panels (left and right) and the following:

vii. The bottom of the back panel contains the Trademark, Distributer and Copyright information in white font. See below:

"The trade dress of this Xyzal® package is subject to trademark protection.
Dist By: Chattem, Inc., a Sanofi Company, Chattanooga, TN 37409-219"
©2017"

Comment: This is acceptable. See section II.A.i.o. for details.

viii. "Canada" is listed as the County of Origin, directly below distributor information on lower right side panel.

Comment: See section II.A.i.p. for details.

ix. Back Label

a. Back (left) Label

The unformatted Drug Facts label content found under the Active ingredient, Purpose, Uses headings, and the Warnings through to Keep out of reach of children subheading is on the left-back panel. A directional arrow leads the reader to the adjacent right back panel.
Comment: See Section II.A.ii.

b. **Back (right) Label**

The back (right) panel continues the unformatted Drug Facts label content from the back (left) panel with the start of Directions, Other Information (storage statement and sodium statement), Inactive ingredients and Questions and comments.

Comment: See section II.A.ii.a-i for details.

C. Dosing Cup and Induction Seal

i. The dosing cup rendering submitted has line markings on both sides for 2.5 mL, 5 mL and 10 mL. The proprietary name "Children's

Xyzal®Allergy 24HR" is on the top of the cup on one side and "Read label directions " and "Wash after use" is on the other side.

Comment: CMC has reviewed this and per correspondence on November 29, 2016, this is acceptable.

ii. The induction seal has the repeated statement, "SEALED for YOUR PROTECTION"

Comment: This is acceptable.

III. RECOMMENDATIONS

Please communicate the following to the sponsor:

A. The following revisions are to be made by the sponsor:

i. Non Drug Facts labeling

a. Update statement of identity (SOI) to bold face on PDP to comply with §201.61 (c).
b. Replace the placeholder "Xs" with actual NDC number to comply with §207.35 (b)(3).
c. Update "ml" to "mL" in statement of identity AND net quantity on carton and immediate container.
d. Update country of origin to "Switzerland (b) (4) as these countries are the manufacturers of API."
e. Revise statement, (b) (4) to "Clinically proven 24 hour relief" on 10-count carton to comply with drug class labeling.
f. Place statement, "Read directions and warnings before use. Keep this carton. It has important information" on carton as this NDA is not marketed with a consumer information leaflet (CIL).
g. Include an image of the dosing cup on the principal display panel of carton labeling. In addition, include an image of the dosing cup on the side panel above the phrase “Use Only With Enclosed Dosing Cup”. The image of cup should appear empty with measurement lines visible.

ii. Drug Facts labeling

a. In *Directions,* change (b) (4) to be consistent with prescription labeling.
b. In *Questions or Comments*?, Replace the placeholder Xs with actual telephone number on cartons and immediate container bottles. We also recommend that the label include the days of the week and times that the toll-free number is in operation.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

6 Page(s) of Draft Labeling 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/

KAREN E LIVORNESE
12/22/2016

KEVIN L LORICK
12/22/2016
I concur with the review and recommendations.

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 16, 2016
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 209089
Product Name and Strength:	Xyzal Allergy 24HR (levocetirizine dihydrochloride) Tablets, 5 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Sanofi US Services Inc., acting as the agent for UCB Inc.
Submission Date:	March 31, 2016
OSE RCM #:	2016-1221
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA 209089 submission, this review evaluates the proposed container labels and carton labeling for Xyzal Allergy 24HR for areas of vulnerability that could lead to medication errors.

Xyzal (levocetirizine dihydrochloride) tablets were first approved on May 25, 2007 under NDA 022064. The Applicant is now seeking a partial prescription to nonprescription switch to market Xyzal Allergy 24HR for the temporary relief of symptoms due to hay fever or other respiratory allergies (runny nose, sneezing, itchy, watery eyes and itching of the nose or throat) for adults 64 years of age and younger and children 6 years of age and older, whereby the chronic idiopathic urticarial indication will remain as a prescription indication.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant intends to market Xyzal Allergy 24HR (levocetirizine dihydrochloride tablets) for the same OTC use as the Children's Xyzal Allergy 24HR, pediatric SKU[a]. In the proposed Xyzal Allergy 24HR container labels and carton labeling, the phrase "[redacted (b) (4)]" is present in place of the modifier "Children's" which is present in the proposed Children's Xyzal Allergy 24HR container labels and carton labeling. The same color scheme is used in the proposed Xyzal Allergy 24HR container labels and carton labeling as in the proposed Children's Xyzal Allergy 24HR container label and carton labeling. We note the prominent multi-color (different shades of orange and blue) curved lines surrounding the proprietary name, Xyzal Allergy 24HR, throughout the container labels and carton labeling; however, this curved lines

[a] The pediatric SKU container and carton for Children's Xyzal Allergy 24HR is evaluated in a separate OSE review. See OSE RCM# 2016-1222.

graphic does not appear to intervene with the proprietary name, thus, we do not anticipate that the proposed graphic presentation would contribute to medication errors.

Our search of FAERS and ISMP did not yield medication error cases relevant to this review. Our review of the proposed container labels and carton labeling for Xyzal Allergy 24HR determined they are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels and carton labeling for Xyzal Allergy 24HR are acceptable from a medication error perspective.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xyzal Allergy 24HR that Sanofi US Services Inc. submitted on March 31, 2016.

Table 2. Relevant Product Information for Xyzal Allergy 24HR	
Initial Approval Date	N/A
Active Ingredient	Levocetirizine dihydrochloride
Indication	Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat
Route of Administration	Oral
Dosage Form	Tablets
Strength	5 mg
Dose and Frequency	(b) (4)
How Supplied	10-count blister in a carton 35-count, 45-count, 55-count, and 80-count bottles 110-count club pack
Storage	Store between 20° and 25°C (68° and 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 29, 2016, we searched the L:drive and AIMS using the terms, Xyzal, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews for the prescription product and 4 reviews related to the proposed proprietary name submissions.[b,c,d,e,f,g] The information in these reviews was not relevant to the proposed OTC product Xyzal Allergy 24HR container labels and carton labeling evaluation. We have not reviewed labels and labeling for Xyzal Allergy 24HR.

[b] Tezky T. Consultation Response for Xyzal IND 72233. Silver Spring (MD): FDA, CDER, OSE, DMETS (US); 2005 OCT 06. RCM No. 05-0312.

[c] Holmes L. Label and Labeling Review for (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 SEP 11. RCM No. 2008-2037.

[d] Jones G. Proprietary Name Review for IND 126506 and IND 126507. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 14. RCM No. 2015-1541618 and 2015-1541620.

[e] Jones G. Proprietary Name Review for IND 126506 and IND 126507. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 14. RCM No. 2015-1541612 and 2015-1541615.

[f] Jones G. Proprietary Name Memorandum for NDA 209090. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 26. RCM No. 2016-3246956

[g] Jones G. Proprietary Name Memorandum for NDA 209089. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 26. RCM No. 2016-3246951.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 30, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Newsletter Community Newsletter Nursing Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Xyzal

D.2 Results

Our search of the ISMP newsletters did not yield any results.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 22, 2016, using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[h]

Table 3: FAERS Search Strategy	
Initial FDA Receive Dates	**None**
Product Name	**Xyzal**
Event (MedDRA Terms)	*Medication errors* SMQ (narrow)

E.2 Results

Our search identified 14 cases. Upon further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

N/A

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[h] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GRACE JONES
12/16/2016

CHI-MING TU
12/16/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 16, 2016
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 209090
Product Name and Strength:	Children's Xyzal Allergy 24HR (levocetirizine dihydrochloride), Oral Solution, 2.5 mg/5 mL
Product Type:	Single-Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Sanofi US Services Inc., acting as the agent for UCB Inc.
Submission Date:	March 31, 2016
OSE RCM #:	2016-1222
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA 209090 submission, this review evaluates the proposed container label and carton labeling for Children's Xyzal Allergy 24HR for areas of vulnerability that could lead to medication errors.

Xyzal (levocetirizine dihydrochloride) oral solution was first approved on January 28, 2008 under NDA 022157. The Applicant is now seeking a partial prescription to nonprescription switch to market Children's Xyzal Allergy 24HR for the temporary relief of symptoms due to hay fever or other respiratory allergies (runny nose, sneezing, itchy, watery eyes and itching of the nose or throat) for adults 64 years of age and younger and children 2 years of age and older, whereby the chronic idiopathic urticarial indication will remain as a prescription indication.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant intends to market the pediatric SKU Children's Xyzal Allergy 24HR (levocetirizine dihydrochloride) oral solution for the same OTC use as the Xyzal Allergy 24HR.[a] In the proposed Children's Xyzal Allergy 24HR container label and carton labeling, the modifier "Children's" replaces the phrase [redacted] (b) (4) which is present in the proposed Xyzal Allergy 24HR container labels and carton labeling. The same color scheme is used in the proposed Children's Xyzal Allergy 24HR container label and carton labeling as in the proposed Xyzal Allergy 24HR container labels and carton labeling. We note the prominent multi-color (different shades of orange and blue) curved lines surrounding the proprietary name, Children's Xyzal Allergy 24HR, throughout the container label and carton labeling; however, this curved

[a] Container and carton for Xyzal Allergy 24HR is evaluated in a separate OSE review. See OSE RCM# 2016-1221.

lines graphic does not appear to intervene with the proprietary name, thus, we do not anticipate that the proposed graphic presentation would contribute to medication errors.

Additionally, though a dosing cup is included, we note the lack of dosing cup image on the proposed Children's Xyzal Allergy 24HR carton labeling. According to FDA Guidance[b], manufacturers should try to ensure that the dosage delivery devices are used only with the products with which they are included by either including a statement on the drug product's bottle, and/or carton labeling, or by using an integrated dosage device. While the statement "use only with enclosed dosing cup" does appear in the Drug Facts, an image of the dosing cup on the principal display panel of carton labeling would better communicate to consumers that there is a dosing cup enclosed and may help increase the awareness that this dosing cup should be used to dose the proposed Children's Xyzal Allergy 24HR.

Our search of FAERS and ISMP did not yield medication error cases relevant to this review. Our review of the proposed container label for Children's Xyzal Allergy 24HR determined it is acceptable from a medication error perspective; however, we provide recommendation for the carton labeling to highlight and increase prominence of important information.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label for Children's Xyzal Allergy 24HR is acceptable from a medication error perspective; however, we provide recommendation for the carton labeling to highlight and increase prominence of important information. Please see our recommendation in section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Carton Labeling
    a. To better communicate to consumers that there is a dosing cup enclosed and to help increase the awareness that this dosing cup should be used to dose the proposed Children's Xyzal Allergy 24HR product, we recommend to include an image of the dosing cup on the principal display panel of carton labeling. Alternatively, include an image of the dosing cup on the side panel above the phrase "Use Only With Enclosed Dosing Cup".

[b] Guidance for Industry: Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products. 2011. Available from http://www.fda.gov/downloads/Drugs/.../Guidances/UCM188992.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

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Active Ingredient	Levocetirizine dihydrochloride
Indication	Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat
Route of Administration	Oral
Dosage Form	Solution
Strength	2.5 mg/5 mL
Dose and Frequency	(b) (4) [redacted]
How Supplied	5 oz. oral solution bottle with dosing cup and foil induction seal
Storage	Store between 20° and 25°C (68° and 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 29, 2016, we searched the L:drive and AIMS using the terms, Xyzal, to identify reviews previously performed by DMEPA.

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Our search identified 2 previous reviews for the prescription product and 4 reviews related to the proposed proprietary name submissions.[c,d,e,f,g,h] The information in these reviews was not relevant to the proposed OTC product Children's Xyzal Allergy 24HR container labels and carton labeling evaluation. We have not reviewed labels and labeling for Children's Xyzal Allergy 24HR.

[c] Tezky T. Consultation Response for Xyzal IND 72233. Silver Spring (MD): FDA, CDER, OSE, DMETS (US); 2005 OCT 06. RCM No. 05-0312.

[d] Holmes L. Label and Labeling Review for (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 SEP 11. RCM No. 2008-2037.

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[f] Jones G. Proprietary Name Review for IND 126506 and IND 126507. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 14. RCM No. 2015-1541612 and 2015-1541615.

[g] Jones G. Proprietary Name Memorandum for NDA 209090. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 26. RCM No. 2016-3246956

[h] Jones G. Proprietary Name Memorandum for NDA 209089. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 26. RCM No. 2016-3246951.

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E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

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E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[i] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Xyzal Allergy 24HR labels and labeling submitted by Sanofi US Services Inc. on March 31, 2016.

- Container label
- Carton labeling
- Dosing cup

G.2 Label and Labeling Images

Container Label

(b) (4)

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[j] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

GRACE JONES
12/16/2016

CHI-MING TU
12/16/2016

Filing Review for Xyzal®Allergy 24HR

SUBMISSION DATE:	March 31, 2016
NDA/SUBMISSION TYPE:	NDA 209089 (Rx-to-OTC switch)
ACTIVE INGREDIENTS:	Levocetirizine dihydrochloride 5 mg
DOSAGE FORMS:	Tablet
SPONSOR:	Sanofi US Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 Cynthia Psaras, PhD, Director, Global Regulatory Affairs 908-981-4874
REVIEWER:	Karen Livornese, RN, MSN, DNDP/ODE IV
TEAM LEADER:	Steven Adah, Ph.D., DNDP/ODE IV
ASSOCIATE DIRECTOR for LABELING	Ruth E. Scroggs, PharmD., DNDP/ODE IV

Submitted Labeling	Representative of Following SKUs
10-count carton (blister) 10-count immediate container (blister)	N/A
35-count carton (bottle) 35-count immediate container (bottle)	N/A
45-count carton (bottle), *Bonus 35 + 10* 45-count immediate container (bottle), *Bonus 35 + 10*	N/A
55-count carton (bottle) 55-count immediate container (bottle)	N/A
80-count carton (bottle) 80-count immediate container (bottle)	N/A
110-count club pack / backer card (55-count X2)	N/A
Bottle seal	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is a New NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	CIL not submitted nor required
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include “prescription strength” or similar statements?	Yes	"original prescription strength"
Do any of the labels include “#1 doctor recommended” or similar endorsement statements?	No	

Issues	Yes/No	Comments
Do any labels include text in a language other than English?	Yes	Submitted foreign language labeling in separate section
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	DMEPA review requested
Does a medical officer need to review any clinical issues?	Yes	This is a New NDA
If SLR, should OPQ also review?	N/A	

Review comments:

- "Original prescription strength" is on label - PM to be aware.

- CMC to confirm established name for the statement of identity.

- Differences compared to Zyrtec OTC under ***Warnings/Do not use/Ask a doctor before use if you have/ Ask a doctor or pharmacist before use if you are***:
    - Xyzal OTC does not include liver disease warning. Neither does Xyzal RX.
    - Xyzal OTC allergic reaction statement language differs from Zyrtec OTC; but it is similar to Xyzal RX.
    - Xyzal OTC includes urinary retention warning as in RX. Zyrtec OTC does not have this warning.
    - ***"Ask a doctor pharmacist before use if you are*** taking tranquilizers or sedatives" is not included in Xyzal OTC labeling. This is included in Zyrtec OTC labeling.

The above comments will be addressed following full review of the submission. From a labeling perspective the submission is filable.

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/s/

KAREN E LIVORNESE
06/03/2016

STEVEN A ADAH
06/03/2016

Filing Review for Xyzal®Allergy 24HR

SUBMISSION DATE:	March 31, 2016
NDA/SUBMISSION TYPE:	NDA 209090 (Rx-to-OTC switch)
ACTIVE INGREDIENTS:	Levocetirizine dihydrochloride 2.5mg / 5mL
DOSAGE FORMS:	Oral Solution
SPONSOR:	Sanofi US Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 Cynthia Psaras, PhD, Director, Global Regulatory Affairs 908-981-4874
REVIEWER:	Karen Livornese, RN, MSN, DNDP/ODE IV
TEAM LEADER:	Steven Adah, Ph.D., DNDP/ODE IV
ASSOCIATE DIRECTOR for LABELING	Ruth E. Scroggs, PharmD., DNDP/ODE IV

Submitted Labeling	Representative of Following SKUs
5 fluid ounce (fl oz) carton (bottle), *Children's Tutti-Frutti Flavor* 5 fluid ounce (fl oz) immediate container (bottle)	N/A
Oral Solution Dosing Cup representation	N/A
Bottle Safety Seal	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is a new NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	CIL not submitted nor required
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include “prescription strength” or similar statements?	No	
Do any of the labels include “#1 doctor recommended” or similar endorsement statements?	No	
Do any labels include text in a language other than English?	Yes	Submitted foreign language labeling in separate section
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	DMEPA review requested
Does a medical officer need to review any clinical issues?	Yes	This is a New NDA
If SLR, should OPQ also review?	No	

Review comments:

- CMC to confirm established name for the statement of identity.

- Differences compared to Zyrtec OTC under ***Warnings/Do not use/Ask a doctor before use if you have/ Ask a doctor or pharmacist before use if you are***:
  - Xyzal OTC does not include liver disease warning. Neither does Xyzal RX.
  - Xyzal OTC allergic reaction statement language differs from Zyrtec OTC; but it is similar to Xyzal RX.
  - Xyzal OTC includes urinary retention warning as in RX. Zyrtec OTC does not have this warning.
  - ***"Ask a doctor pharmacist before use if you are*** taking tranquilizers or sedatives" is not included in Xyzal OTC labeling. This is included in Zyrtec OTC labeling.

The above comments will be addressed following full review of the submission. From a labeling perspective the submission is filable.

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/s/

KAREN E LIVORNESE
06/03/2016

STEVEN A ADAH
06/03/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA #209089 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Xyzal Allergy 24HR Established/Proper Name: levocetirizine dihydrochloride Dosage Form: tablet Strengths: 5 mg		
Applicant: UCB, Inc. Agent for Applicant (if applicable): Sanofi US Services Inc.		
Date of Application: March 31, 2016 Date of Receipt: March 31, 2016 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: January 31, 2016	Action Goal Date (if different):	
Filing Date: May 30, 2016	Date of Filing Meeting: May 13, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☒ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Uses: Temporarily relieves these symptoms due to hay fever or other respiratory allergies: runny nose; itchy, watery eyes; sneezing; itching of the nose or throat		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☒ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): Division of Pulmonary Allergy and Rheumatology Products (DPARP)	
List referenced IND Number(s): IND 126506; NDA 22064	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also,***	☒	☐		

ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		Paid ½ fee: $1,187,100.00

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**

Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested:	☐	☒	☐	

Note: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	**Note:** This is a single enantiomer of a racemic drug previously approved for the same use; however, it is a partial Rx-to-OTC switch so the levo-enantiomer was previously approved.
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1]	☒	☐	☐	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.

If not, explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	☒	☐		The clinical reviewer stated that the NDA was somewhat confusing in the way it was indexed, but would be reviewable.
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☐	☐		No new clinical studies were

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				conducted so no new financial disclosure forms are required.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☒		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

REMS	YES	NO	NA	Comment
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		
Is the PI submitted in PLR format?[4]	☐	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☐ ☐	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: **If PI not submitted in PLLR format**, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

(*send WORD version if available*)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☒ Blister card ☒ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 1, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		IND 126506-A so-called Pre-IND meeting was held on October 1, 2015, however Pre-NDA topics were discussed.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 13, 2016

BACKGROUND: This is a partial Rx-to-OTC switch of Xyzal tablets. The indications for allergic rhinitis are being switched to OTC. The Chronic Iodiopathic Urticaria indication will remain Rx.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sherry Stewart	Y
	CPMS/TL:	Dan Brum	phone
Cross-Discipline Team Leader (CDTL)	Jane Filie		Y
Division Director/Deputy	Theresa Michele		Y
Office Director/Deputy	Charles Ganley		N
Clinical	Reviewer:	Brenda Gierhart	Y
	TL:	Jane Filie	Y
Social Scientist Review (*for OTC products*)	Reviewer:	Amanda Pike-McCrudden	Y
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Karen Livornese	Y
	TL:	Steve Adah	N
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Bavna Saluja	Y
	TL:	Anshu Marathe	phone
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics (review consumer studies)	Reviewer:	Rongmei Zhang	Y

	TL:	Rima Izem	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Charlie Thompson	phone
	TL:	Jane Sohn	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Swapan De	Y
	RBPM:	Thao Vu	phone
• Drug Substance	Reviewer:	Sam Bain	N
• Drug Product	Reviewer:	Sam Bain	N
• Process	Reviewer:	Tarun Mehta	N
• Microbiology	Reviewer:	Tarun Mehta	N
• Facility	Reviewer:	Tony Wilson	N
• Biopharmaceutics	Reviewer:	An-Chi Lu/Albert Chen	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Danae Christoulou		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Grace Jones	N
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	DPARP Clinical-Anthony Durmowicz		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	This is an Rx-to-OTC switch so a bridge is not necessary. Product is identical to RX product.
• Per reviewers, are all parts in English or English translation? **If no**, explain: Note that foreign labels were also included in the submission.	☒ YES ☐ NO

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No additional clinical studies were conducted.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Many products already approved in this class of drugs. No apparent novel safety or efficacy concerns that would benefit from discussion an at AC meeting.
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Label comprehension study will be reviewed by the consumer stats group.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Theresa Michele **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

SHERRY A STEWART
05/16/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA #209090 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Xyzal Allergy 24HR Established/Proper Name: levocetirizine dihydrochloride Dosage Form: oral solution Strengths: 2.5 mg/5 mL (0.5 mg/mL)		
Applicant: UCB, Inc. Agent for Applicant (if applicable): Sanofi US Services Inc.		
Date of Application: March 31, 2016 Date of Receipt: March 31, 2016 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: January 31, 2016	Action Goal Date (if different):	
Filing Date: May 30, 2016	Date of Filing Meeting: May 13, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☒ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Uses: Temporarily relieves these symptoms due to hay fever or other respiratory allergies: runny nose; itchy, watery eyes; sneezing; itching of the nose or throat		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☒ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): Division of Pulmonary, Allergy and Rheumatology Products (DPARP)	
List referenced IND Number(s): IND 126506; NDA 22064	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also,***	☒	☐		

ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		Paid ½ fee: $1,187,100.00

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**

Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested:	☐	☒	☐	

Note: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	**Note:** This is a single enantiomer of racemic drug previously approved for the same use; however it's a partial Rx-to-OTC switch so the levo- enantiomer was previously approved.
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1]	☒	☐	☐	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.

If not, explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	☒	☐		The clinical reviewer stated that the NDA was somewhat confusing in the way it was indexed, but that it would be adequate for review.
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		No new clinical studies were

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				conducted so no new financial disclosure forms are required.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☒		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	

2 http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

3 http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

REMS	YES	NO	NA	Comment
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		
Is the PI submitted in PLR format?[4]	☐	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☐ ☐	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: **If PI not submitted in PLLR format**, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

(*send WORD version if available*)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☒ Other (specify) Dosing cup, induction seal			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 1, 2015. ***If yes, distribute minutes before filing meeting***	☒	☐		IND 126507-A so-called pre-IND meeting was held on October 1, 2015; however Pre-NDA topics were discussed.
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

If yes, distribute letter and/or relevant minutes before filing meeting				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 13, 2016

BACKGROUND: This is a partial Rx-to-OTC switch of Xyzal (levocetirizine dihydrochloride) oral solution. The indications for allergic rhinitis are being switched to OTC. The Chronic Iodiopathic Urticaria indication will remain Rx.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sherry Stewart	Y
	CPMS/TL:	Dan Brum	phone
Cross-Discipline Team Leader (CDTL)	Jane Filie		Y
Division Director/Deputy	Theresa Michele		Y
Office Director/Deputy	Charles Ganley		N
Clinical	Reviewer:	Brenda Gierhart	Y
	TL:	Jane Filie	Y
Social Scientist Review (*for OTC products*)	Reviewer:	Amanda Pike-McCrudden	Y
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Karen Livornese	Y
	TL:	Steve Adah	N
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Bavna Saluja	Y
	TL:	Anshu Marathe	phone
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics (review of consumer studies)	Reviewer:	Rongmei Zhang	Y

	TL:	Rima Izem	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Charlie Thompson	phone
	TL:	Jane Sohn	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Swapan De	Y
	RBPM:	Thao Vu	phone
• Drug Substance	Reviewer:	Sam Bain	N
• Drug Product	Reviewer:	Sam Bain	N
• Process	Reviewer:	Tarun Mehta	N
• Microbiology	Reviewer:	Tarun Mehta	N
• Facility	Reviewer:	Tony Wilson	N
• Biopharmaceutics	Reviewer:	An-Chi Lu/Albert Chen	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Danae Christoulou		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Grace Jones	N
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	DPARP Clinical-Anthony Durmowicz		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO This is an Rx-to-OTC switch so a bridge is not necessary. Product is identical to RX product.
• Per reviewers, are all parts in English or English translation? **If no**, explain: Note that foreign labels were also included in the submission.	☒ YES ☐ NO

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No additional clinical studies were conducted.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Many products already approved in this class of drugs. No apparent novel safety or efficacy concerns that would benefit from discussion at an AC meeting.
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Label comprehension study will be reviewed by the consumer stats group.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Theresa Michele **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

APPEARS THIS WAY ON ORIGINAL

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

/s/

SHERRY A STEWART
05/16/2016