CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212268Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212268
Review #1

Drug Name/Dosage Form	SECUADO (Asenapine) Transdermal System
Strength	3.8, 5.7 and 7.6 mg/24 hours
Route of Administration	Transdermal
Rx/OTC Dispensed	Rx
Applicant	Hisamitsu Pharmaceutical Co., Inc.
US agent, if applicable	Noven Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	*12/13/2018*	*all*
0002	*1/16/2019*	*All (samples)*
0004	*2/6/2019*	*Drug Substance*
0005	*2/11/2019*	*Facilities*
0006	*2/26/2019*	*Transdermal Group*
0008	*3/05/2019*	*Drug Substance / Facilities*
0009	*3/20/2019*	*Process*
0011	*3/28/2019*	*Drug Product*
0012	*4/08/2019*	*Process*
0015	*4/22/2019*	*Drug Product*
0016	*4/28/2019*	*OTR*
0018	*5/08/2019*	*Biopharm*
0019	*5/15/2019*	*Process*
0020	*5/21/2019*	*Process*
0021	*5/29/2019*	*Drug Product*
0022	*6/12/2019*	*Drug Product*
0024	*6/19/2019*	*OTR*
0025	*6/21/2019*	*Drug Substance*
0026	*7/01/2019*	*Drug Product / Process*
0027	*7/03/2019*	*Drug Product / Process*
0028	*7/08/2019*	*Drug Substance*

0028	*7/15/2019*	*Process*
0030	*7/19/2019*	*Biopharm*
0035	*8/19/2019*	*Biopharm*
0036	*8/23/2019*	*Drug Product*
0038	*8/30/2019*	*Biopharm*
0039	*9/03/2019*	*Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Ray Frankewich	Su Tran
Drug Product	Andei Ponta	Wendy Wilson-Lee
Process	James Norman	Yubing Tang
Facility	James Norman	Yubing Tang
Biopharmaceutics	Kaushalkumar Dave	Ta-Chen Wu
Quality InVivo Adhesion	Le Zhang	Caroline Strasinger
Adhesion Study Biostatistics	Chao Wang, Ph.D.	Meiyu Shen, Ph.D.
Laboratory (OTR)	Anna Wokovich, Laura Pogue	Jason Rodriguez
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Asenapine is currently marketed only as a sublingual tablet dosage form (Saphris). Saphris is indicated for the treatment of schizophrenia (in adults) as well as for the acute treatment (as monotherapy or adjunctive therapy) of manic or mixed episodes associated with bipolar disorder. Its labeled dosage is 5 mg or 10 mg, twice daily

This 505(b)(2) application proposes the marketing of Secuado (asenapine) transdermal system for the treatment of schizophrenia in adults, referencing Saphris NDA 22117 as the listed drug. Marketing of four strengths is proposed: (b) (4), 5.7 mg/24 hours or 7.6 mg/24 hours. The strengths are compositionally proportional with just the size (area) differing - 20 cm^2, 30 cm^2 and 40 cm^2, respectively. The maximum daily dose is 7.6 mg/24 hours. The transdermal system releases asenapine over 24 hours and is designed to be applied once daily (then removed) to one of the following sites: hip, abdomen, upper arm, or upper back area. Data from two clinical adhesion studies demonstrated adequate in vivo adhesion for the prescribed 24-hour wear period for all the tested adhesion sites, except for the upper chest site. (b) (4) .

The transdermal system is a translucent rounded square with a printed backing on one side and a release liner on the other. The printing includes the strength of the transdermal system. The drug product is supplied in an individual pouch. Thirty pouches are placed in a carton for a one-month supply. The proposed room temperature 24-month expiry was found to be adequately supported by stability data.

The drug product contains more than the labeled amount of drug as studies found that ca. (b) (4) % of the drug is released from the patch after 24 hours of application (b) (4) % in HP-3070-US-01 study). The transdermal system exposed to heat released approximately 7% more drug over 24 hours.

Proposed Indication(s) including Intended Patient Population	Treatment of schizophrenia in adults
Duration of Treatment	*Chronic*

Maximum Daily Dose	*7.6 mg*
Alternative Methods of Administration	*None.*

B. Quality Assessment Overview

Drug Product: Hisamitsu Pharmaceutical developed Secuado (asenapine) transdermal system for the treatment of schizophrenia in adults. The transdermal system releases asenapine over 24 hours and is designed to be applied once-daily to one of the following sites: hip, abdomen, upper arm, or upper back area.

Marketing of four strengths is proposed: (b) (4) 5.7 mg/24 hours or 7.6 mg/24 hours. The strengths are compositionally proportional with just the size (area) differing - 20 cm^2, 30 cm^2 and 40 cm^2, respectively. The maximum daily dose is 7.6 mg/24 hours

The transdermal system is a translucent rounded square with a printed backing on one side and a release liner on the other. The printing includes the strength of the transdermal system. The drug product is supplied in an individual pouch. Thirty pouches are placed in a carton for a one-month supply. The proposed room temperature 24-month expiry was found to be adequately supported by stability data.

(b) (4)

(b) (4)

(b) (4)

The applicant also developed a training product with no drug. This is 20 cm^2 - equivalent to the lowest strength in size. It is proposed for use as demonstration material. The excipients, manufacturing process, and packaging material are the same as the proposed commercial drug product. The Applicant cross-references all chemistry, manufacturing, and controls information to DMF #30096. A letter of authorization has been provided as part of the submission. The DMF is currently active and up to date. The analytical methods were found acceptable by the review team. OPF OTR attempted to verify several methods and comments forwarded to the applicant (attachments).

A categorical exclusion claim for submission of an environmental assessment was made based on 21 CFR Part 25 and has included a statement of no extraordinary circumstances, in accordance with 21 CFR 25.15.

Process/Facilities: The drug substance site and drug substance intermediate site were found acceptable by OPF. A PAI was carried out at the drug product manufacturing site in May 2019 and it was found acceptable. There were no outside testing facilities listed in the submission.
The manufacturing process uses the following major unit operations: (b) (4)

After multiple rounds of information requests, the manufacturing process and controls were found adequate. OPF recommended approval from process, facility, and microbiology perspectives.

Drug substance: (b) (4)

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Biopharmaceutics: (b) (4)

(b) (4)

The **adhesion properties** of the product were supported by a clinical adhesion study, HP-3070-US-08. The results of another less complete adhesion study (HP-3070-GL-04 were used as supportive data for *in vivo* adhesion. These data were assessed by an OPQ team in consultation with a team from the Office of Biostatistics (see attached reviews). Data from both studies demonstrated adequate in vivo adhesion for the prescribed 24-hour wear period for all of the tested adhesion sites, except for the upper chest site. (b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

See attached labeling review, including listing the active ingredient as asenapine base not asenapine (b) (4).

David Claffey

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

(b) (4)

(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Secuado (asenapine), transdermal system
Dosage form, route of administration	Transdermal system, transdermal
Controlled drug substance symbol	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Transdermal System: 3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours.

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

(b) (4)

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation	Yes, the product is to be applied on a clean, dry and intact skin at the selected application site. Application sites include: the upper arm, upper chest, upper back, abdomen or hip. Reviewer's Note: (b) (4) If the the transdermal system has lifted at the edges, patients are to reattach SECUADO by pressing firmly and smoothing down the edges of the system After use, instruct patients are to fold used SECUADO so that the adhesive side sticks to

	itself and safely discard where children and pets cannot get to it. (b) (4) [redacted]

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

SECUADO is a translucent transdermal system that is available in 3 dosage strengths.

Table 1: Dosage Strengths

Dosage Strength (Nominal Dose Delivered)	Asenapine Content per System	Transdermal System Size
3.8 mg/24 hours	6.4 mg	20 cm^2
5.7 mg/24 hours	9.6 mg	30 cm^2
7.6 mg/24 hours	12.8 mg	40 cm^2

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Transdermal system
Strengths: in metric system	Transdermal System: 3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours. Reviewer's Note: Applicant will be asked to remove the table and include only the nominal dose delivered (labeled strength)
Active moiety expression of strength with equivalence statement	Asenapine
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A translucent rounded square patch with a printed backing on one side and a release liner on the other. The print on the backing is "Secuado® (asenapine) transdermal system X mg/24 hours" Reviewer's Note: Applicant will be asked to include a description of the transdermal system

Is the information accurate? ☒ Yes ☐ No

4. *Section 11 Description*

(b) (4) [redacted]

(b) (4)

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Secuado (asenapine), transdermal system
Dosage form and route of administration	Transdermal System: 3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours.
Active moiety expression of strength with equivalence statement (if applicable)	Asenapine
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The drug product contains the following excipients: styrene-isoprene-styrene block copolymer, polyisobutylene, alicyclic saturated hydrocarbon resin, mineral oil, sodium acetate anhydrous, isopropyl palmitate, butylated hydroxytoluene, polyester film backing and silicone-treated polyester release liner. Reviewer's Note: Applicant will be asked to reorder the excipients so that they are in alphabetical order and to to include the maleate salts (b) (4) as part of the excipients.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Atypical antipsychotic
Chemical name, structural formula, molecular weight	$C_{17}H_{16}ClNO$ – (b) (4) Reviewer's Note: (b) (4)
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical	(b) (4)

properties (such as pKa or pH)	

Is the information accurate? ☒ Yes ☐ No

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

(b) (4)

[redacted]

(b) (4)

[redacted]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Transdermal System: 3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours.
Available units (e.g., bottles of 100 tablets)	Carton of 30 systems
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A translucent rounded square patch with a printed backing on one side and a release liner on the other. The print on the backing is "Secuado® (asenapine) transdermal system X mg/24 hours" Reviewer's Note: Applicant will be asked to include this information in the label

Special handling	Not Applicable
Storage conditions	USP controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Hisamitsu Pharmaceutical Co., Inc.

Reviewer's Assessment of Package Insert: ***Adequate***

Prescribing Information complies with all regulatory requirements from a CMC perspective.

However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations.

II. Labels:

1. ***Carton Labels***

(b) (4)

(b) (4)

Item	Information provided in the pouch label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Secuado (asenapine) transdermal system Reviewer's Note: Applicant will be asked to remove "patch" from all labeling and label (including carton container)
Dosage strength	Complies
Net contents	Complies
"Rx only" displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies
Lot number and expiration date (21 CFR 201.17)	Complies
Storage conditions	Complies
Bar code (21CFR 201.25)	Not included Reviewer's Note: Applicant will be asked to include this information in the label
Name of manufacturer/distributor	Complies
And others, if space is available	Not Applicable

Reviewer's Assessment of Labels: ***Adequate***

The container labels comply with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

However, there is no space for a bar code on the primary pouch. This will be communicated to the Applicant as part of DNP labeling negotiations.

4. ***Placebo***

(b) (4)

(b) (4)

Item	Information provided in the pouch label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Demonstration Sample Reviewer's Note: Applicant will be asked to remove "patch" from all labeling and label (including carton container) Applicant will also be asked to remove Secuado (asenapine) transdermal system from the label
Dosage strength	Complies (contains no active)
Net contents	Complies
"Rx only" displayed prominently on the main panel	NA – demonstration use only
NDC number (21 CFR 207.35(b)(3)(i))	NA – demonstration use only
Lot number and expiration date (21 CFR 201.17)	Complies
Storage conditions	Complies
Bar code (21CFR 201.25)	Not included Reviewer's Note: Applicant will be asked to include this information in the label
Name of manufacturer/distributor	Complies
And others, if space is available	Not Applicable

Reviewer's Assessment of Labels: ***Adequate***

The placebo label complies with regulatory requirements from a CMC perspective.

However, there is no space for a bar code on the primary pouch. This will be communicated to the Applicant as part of DNP labeling negotiations.

List of Suggested Edits Communicated to Applicant:

1. *Include the description of the transdermal system in the dosage form and strengths section*
2. *In the dosage form and strengths section, remove the table and include only the nominal dose delivered (labeled strength). The remaining information should be moved to the description section.*
3. *In Section 16, Storage and handling, include an identification of the dosage form (e.g., shape, color, coating, scoring, imprinting).*
4. *Ensure that the excipients are listed in alphabetical order in the PI.*

5. *Ensure all uses of the word "patch" are replaced with "system" or the name of the product as appropriate throughout the PI and carton and container.*

6. *Provide a space for a bar code on the primary pouch for the drug products and the placebo.*

7. *Remove Secuado (asenapine) transdermal system from the demonstration sample label*

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

Application No: NDA 212268; 505(b)(2)
Drug Product Name/Strengths: Asenapine Transdermal System; 3.8, 5.7, and 7.6 mg/24 hours
Route of Administration: Transdermal
Indication: Treatment of Schizophrenia
Applicant Name: Hisamitsu Pharmaceutical Co., Inc.
Date of Submission: 12/13/2018 (Original)

Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Ta-Chen Wu, PhD

REVIEW SUMMARY

Submission: The Applicant submitted the NDA for Asenapine Transdermal System (TDS), 3.8/24 hours, 5.7/24 hours, and 7.6 mg/24 hours (also referred as HP-3070) under the 505(b)(2) pathway with its reliance on the prior safety and efficacy findings of the Agency for the Listed Drug (LD) Saphris® (asenapine) Sublingual Tablets (NDA 022117, approved on August 13, 2009). The proposed TDS drug product is indicated for the treatment of schizophrenia. Asenapine (b) (4) is an atypical antipsychotic drug that belongs to the dibenzo-oxepino pyrrole class. HP-3070 is a once a day TDS applied for 24 hours that has been formulated at dose levels ranging from (b) (4) to (b) (4).

Review Objective: The Biopharmaceutics review is focused on the evaluation of (1) the proposed in vitro drug release testing (IVRT) method and acceptance criteria, and (2) formulation bridging.

IVRT Method: The Applicant conducted various studies and provided justifications for selection of the suitable IVRT testing conditions. (b) (4)

IVRT Acceptance Criteria: (b) (4)

(b) (4)

FDA approved IVRT method and acceptance criteria for the proposed product

(b) (4)

(b) (4)

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 212268 for Asenapine Transdermal System, 3.8, 5.7, and 7.6 mg/24 hours, is adequate and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	12/13/2018	Original NDA Submission
0018	05/08/2019	Clinical Pharmacology/Response to Information Request
0030	07/19/2019	Quality/Response to Information Request
0035	08/19/2019	Quality/Response to Information Request

BACKGROUND

Hisamitsu has developed four strengths (expressed as mg of asenapine (b) (4) of the once-daily HP-3070 TDS, i.e., (b) (4)), (b) (4) (20 cm^2), (b) (4) (30 cm^2), and (b) (4) (40 cm^2). The four strengths of the proposed product of (b) (4) formulation are compositionally equivalent, cut from the same laminate and varied only in their size. The differences in dose are obtained by the proportional increases in the surface area (size) of the TDS between (b) (4) and 40 cm^2 (Table 1).

Table 1. Dosage strengths for the proposed product

Patch Size	Asenapine (b) (4)	Asenapine (b) (4)	
	Dose (Content per Patch)	**Dose (Content per Patch)**	**Dosage Strength (Nominal Dose Delivered)**
(b) (4)	(b) (4)		
20 cm^2	(b) (4)	6.4 mg	3.8 mg/24 hours
30 cm^2		9.6 mg	5.7 mg/24 hours
40 cm^2		12.8 mg	7.6 mg/24 hours

[a] Included for reference purposes only. This dose is not proposed dosage strength for marketing.
Note: In these calculations, a molecular weight of (b) (4) and 285.77 g/mol were used for asenapine (b) (4) and asenapine free base, respectively.

To support the NDA, the Applicant conducted a pivotal 505(b)(2) PK bridging study [a relative bioavailability (BA) study (Study HP-3070-US-05)] between HP-3070 patch and Saphris (LD) using the HP-3070-(b) (4) ((b) (4) 24 hours) dose in healthy volunteers due to the tolerability issues at higher doses in healthy subjects. In addition to the pivotal PK bridging study, the Applicant conducted Study HP-3070-US-02b to show that asenapine Cmax and AUC values from (b) (4) 24 hours dose and three commercial formulation strengths, i.e., 3.8 mg/24 hours (20 cm2), 5.7 mg/24 hours (30 cm2), and 7.6 mg/24 hours (40 cm2), are dose-proportional.

Efficacy and safety were demonstrated in the pivotal Phase 3 study (HP-3070-GL-04) with 3.8 and 7.6 mg/24 hours doses (5.7 mg/24 hours dose was not evaluated). However, drug exposures for this (5.7 mg/24 hours) dose are within the range of those from 3.8 and 7.6 mg/24 hours HP-3070 doses. The Applicant stated that the selection of doses to be evaluated in the Phase 3 study was discussed and agreed upon by the Agency at the End-Of-Phase 2 meeting (2015 JUN 25).

The Biopharmaceutics review is focused on the evaluation of the (1) proposed in vitro drug release testing (IVRT) method and acceptance criteria, and (2) formulation bridging, as presented below.

PROPOSED IVRT METHOD AND METHOD DEVELOPMENT

(b) (4)

For selection of the proposed IVRT study conditions, the Applicant performed the following studies:

(b) (4)

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Kaushalkumar Dave

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