

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-117

CHEMISTRY REVIEW(S)

Saphiris
(asenapine) sublingual tablets
NDA 22-117

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Organon USA, Inc.
56 Livingston Ave.
Roseland, NJ 07068

Indication: Schizophrenia and acute manic or mixed episodes associated with Bipolar 1 disorder.

Presentation: Saphris® (asenapine) Sublingual Tablets are available in two strengths as round, white to off-white fast dissolving sublingual tablets at 5 mg strength (with “5” on one side) or 10 mg strength (with “10” on one side) and packaged in blisters. Boxes of 60 contain 6 blisters of 10 tablets; boxes of 100 contain 10 blisters of 10 tablets.

EER Status: Acceptable, 11-MAR-08

Consults: Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Original Submission: 30-AUG-2007

Post-Approval Agreements: None

Drug Substance

The drug substance, asenapine maleate, is a small, synthetic, new molecular entity (NME) with an empirical formula of $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ and a molecular weight of 401.84 (free base: 285.8). Known chemically as (3aRS,12bRS)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenzo[2,3:6,7]oxepino[4,5-c]pyrrole (2Z)-2-butenedioate (1:1), it is white to off-white powder that melts at about 139.9 °C. It is slightly soluble in water (3.7 mg/mL), displaying a pH of 4.6, and freely soluble in methanol, ethanol, and acetone. The pKa of the protonated base is 8.6. The molecule has two chiral centers but is being developed as the racemate. (b) (4) polymorphs have been found: (b) (4) is the most stable form at ambient temperature as the drug substance; (b) (4) is the most stable at high temperature. In addition, (b) (4) pseudopolymorphs were observed.

The manufacture of asenapine maleate is a (b) (4) process proceeding from a (b) (4) to yield the final drug substance.

The structure of asenapine maleate was

(b) (4)

The proposed release specification for asenapine maleate includes: appearance, color, visible impurities, identification by IR, identification by (b) (4) High Performance Liquid Chromatography (RP-HPLC), (b) (4)

(b) (4). The reference standard is manufactured using the (b) (4) manufacturing process and has been adequately tested and meeting more stringent specification. Impurity reference standards have likewise been synthesized and characterized.

Adequate stability data were provided to support a (b) (4) retest date for the bulk drug substance, stored at controlled room temperature, inside (b) (4) bags contained in a barrel.

Conclusion: Drug substance is satisfactory

Drug product

Saphris® (asenapine) Sublingual Tablets are available in two strengths as round, white to off-white fast dissolving sublingual tablets at 5 mg strength (with “5” on one side) or 10 mg strength (with “10” on one side) and packaged in blisters.

The drug product is manufactured by the following steps:

(b) (4)

The composition of the 5 mg strength tablet is asenapine maleate (b) (4) gelatin NF (b) (4) and mannitol USP (b) (4) to give a total tablet weight of (b) (4). The composition of the 10 mg strength tablet is asenapine maleate (b) (4) gelatin NF (b) (4) and mannitol USP (b) (4) to give a total tablet weight of 30.47 mg.

Specification of the drug product includes: appearance, identification by (b) (4)-HPLC, identification by UV, assay (b) (4)

Asenapine maleate tablets are packaged in (b) (4) aluminum blister packs. The pockets are debossed to indicate the tablet strength. The asenapine maleate tablets will be packaged in blisters, 10 blisters per card, 6 cards per carton (Child-resistant packaging) or 10 cards per carton (Hospital Unit Dose).

Adequate stability data were provided to support the proposed expiration dating of 24 months at room temperature, 59° - 86°F (15° - 30°C) for the drug product packaged in (b) (4) aluminum blister packs.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested

Overall Conclusion: From a CMC perspective, the application is recommended for approval.

Christine M. V. Moore, Ph.D.
Acting Director, DPA I/ONDQA

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

/s/

Christine Moore
7/17/2009 04:50:47 PM
CHEMIST

NDA 22-117

SAPHRIS[®] (asenapine) Sublingual Tablets

Organon USA Inc.

Chhagan G. Tele, Ph.D.

**Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment**

**Division of Psychiatry Products
Review of Chemistry, Manufacturing, and Controls**

Table of Contents

DIVISION OF PSYCHIATRY PRODUCTS	1
Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability.....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and drug substance(s).....	6
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Chemistry Assessment	11

Chemistry Review Data Sheet

1. NDA: 22-117
2. REVIEW #: 3
3. REVIEW DATE: 25-FEB-2009
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-AUG-2007
Amendment #0007: Postapproval Stability Protocol and Commitment, Responses to CMC Information Request, and Catagorical Exclusion	10-DEC-2007
Amendment #0008: Revised draft carton and container labeling, (b) (4)	21-DEC-2007
Amendment #0009: Information on the antistatic agent in LDPE bags used in DS package	21-DEC-2007
Amendment #0014: Describes the liding foil used in blister packaging missing in NDA	17-JAN-2008
Amendment #0015: Information on the exclusion of DS Manufacturing site: N.V. Organon, Vlijtseweg 130, 7317 AK Apeldoorn, The Netherlands	30-JAN-2008
Amendment #0017: Blister foil labeling for both 5 and 10 mg sublingual tablets that will be printed to support product launch	21-FEB-2008
Amendment #0022: Amended DP manufacturing process description	18-APR-2008
Amendment #0024: Response to CMC comments, IR letter 08-APR-08	30-APR-2008
CMC Memo to File	20-JUN-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #0039: Class 1 Resubmission: Response to CR letter 13-JAN-09	12-FEB-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon USA Inc.
Address:	56 Livingston Ave., Roseland, NJ 07068
Representative:	June Bray, Vice President, Regulatory Affairs
Telephone:	(973) 422-7201

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Saphris®
b) Non-Proprietary Name (USAN-2002): asenapine maleate
c) Code Name/# (ONDC only): Org 5222
d) Chem. Type/Submission Priority (ONDC only):
 • Chem. Type: 1
 • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1); Saphris® (asenapine) Sublingual Tablets (5 mg and 10 mg Strengths)

10. PHARMACOL. CATEGORY: For the treatment of Schizophrenia and treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

11. DOSAGE FORM: Tablets (sublingual)

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 SPOTS product – Form Completed
 X Not a SPOTS product

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

USAN Name (2002): asenapine maleate

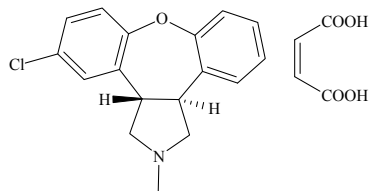
Non-Proprietary Name: (3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1)

Chemical Formula: C₁₇H₁₆ClNO.C₄H₄O₄

Molecular Weight: 401.84

CAS registry #: 85650-56-2; 65576-45-6 (asenapine)

Structure:



Asenapine maleate (Org 5222) contains two chiral centers. Asenapine maleate is a racemate.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	LOA 03-MAR-06

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51,641 (effective 30-SEP-1998) Sublingual Tablets	Commercial IND (Schizophrenia)
IND	70,329 (effective 03-AUG-2004) Sublingual Tablets	Commercial IND (Bipolar disorder)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation	11-MAR-08	Shawnte L. Adams (HFD-322)
Pharmtox	AE	30-APR-08	Elzbieta Chalecka-Franaszek, Ph.D.
Biopharm	Pending		Ron Kavanagh, Ph.D.
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	Pending		
EA	Acceptable, categorical exclusion granted as per information from Organon USA Inc. in this NDA	As per this review	Chhagan G. Tele, Ph.D. (ONDQA-Branch I)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 22-117

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant provided acceptable responses for the CMC comments stated in the CR letter dated 13-JAN-09. However, for the comment provided in CMC Review #2, it is indicated by Dr. Barry Rosloff, pharmtox supervisor (see e-mail dated 24-JUN-08 in the Chemistry Assessment section) and agreed by the Division that the impurity (b) (4) issue would be raised as a PMC (Post Marketing Commitment). From the CMC point of view NDA 22-117 for Saphris® (asenapine) Sublingual Tablets is recommended **APPROVAL**.

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

None as per this review

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and drug substance(s)

General Product Information

Asenapine maleate (Company code: Org 5222) is a novel psychopharmacologic agent belonging to the group of dibenzoxepinopyrrolidine compounds. The active entity of asenapine maleate is asenapine. The proposed trade name for drug product is Saphris®. Asenapine maleate exhibits high affinity and potency for blocking dopamine, serotonin, α -adrenergic and histamine receptors, and no appreciable activity at muscarinic and cholinergic receptors. The applicant claims that the rank order of receptor affinity for asenapine maleate reveals a unique human receptor binding signature, characterized by strong serotonergic properties, when compared to other antipsychotic drugs. Clinical development of asenapine maleate as an antipsychotic was started using a conventional oral formulation. However, this development was discontinued due to unexpected low bioavailability, caused by extensive first-pass metabolism in the liver and (probably) the gut. The bioavailability of orally taken asenapine maleate was more than 20 times lower than taken sublingually (respectively <2% versus 35%). Therefore, a sublingual formulation was developed to circumvent the hepato-gastro-intestinal first-pass metabolism. The applicant used (b) (4) technology to develop asenapine maleate sublingual tablets. (b) (4)

The recommended dose for the treatment of schizophrenia is 5 mg BID and 10 mg BID for the treatment of bipolar disorder.

Drug Product

The drug substance, asenapine maleate (New Molecular Entity) used for the manufacture of Saphris Sublingual Tablets has been studied in commercial IND 51,641 (effective 30-SEP-1998) for the treatment of schizophrenia patients and IND 70,329 (effective 03-AUG-2004) for the treatment of bipolar disorder patients by Organon. For a period of time asenapine maleate was co-developed by

Chemistry Assessment Section

both Organon and Pfizer (Organon no longer collaborating now with Pfizer). Asenapine maleate has not yet been approved for marketing in any country.

Asenapine maleate sublingual tablets will be available in two strengths, 5 mg and 10 mg. The 5 mg and 10 mg strengths are white to off-white circular tablets debossed with "5" or "10" on one side, respectively. Adequate information on components and composition of the proposed commercial drug product for unit dose formulation for two strengths is provided. Common excipients (gelatin and mannitol) of USP/NF/Ph. Eur or JP compendial grades are used to manufacture drug product. The manufacture of the drug product consists of (b) (4) proprietary manufacturing process: (b) (4)

Adequate information was provided for the manufacturing, release, and stability of the registration batches of the drug product from (b) (4) site. Information about controls of critical steps in the manufacture of registration batches of the Saphris Tablets is provided. In-process tests (b) (4) were performed to maintain consistent manufacture of the drug product. The specifications for tablets included Description (Appearance: visual), Identification (UV, HPLC), Assay (HPLC), Impurities (HPLC), Disintegration, Content Uniformity (HPLC), and Water content. Validated analytical methods were provided in the submission. The asenapine maleate tablets will be packaged as: Child-resistant packaging-Box of 60: 6 blisters with 10 tablets (5 mg and 10 mg) and Hospital Unit Dose-Box of 100: 10 blisters with 10 tablets.

The release specification for assay of asenapine maleate tablets by HPLC is (b) (4) of label claim. A specific, stability indicating HPLC method and acceptance criteria have been developed for determination of identification, assay, and purity of asenapine maleate in Saphris Tablets. The HPLC method is specific, with absence of interference from potential degradation products and impurities in the drug product. Assay specification for active ingredient is supported by values observed during release and stability studies of the drug product. This method has been validated with respect to specificity, linearity, working range, accuracy, method precision, limit of detection, and limit of quantitation. The purity acceptance criteria conformed to the limits of purity/degradation products observed during release and ongoing stability studies of Saphris Tablets. Content Uniformity was performed using HPLC method. The proposed specification for Content Uniformity conforms to compendial USP <905> criteria and it is acceptable. Acceptance criteria for both strengths for the individual degradation product (b) (4), unspecified each individual impurities, and total degradation products to the levels that are not consistent with data. The acceptable limits for impurities/degradation product should not be based on strength. The acceptance limit for unspecified each individual degradation product are different, (b) (4)

(b) (4) based on maximum daily dose of 20 mg/day. Similarly degradation product (b) (4) is the metabolite of asenapine in animals and humans with a structural alert for mutagenicity. The acceptance limit for this degradant is different for both strengths, (b) (4) for 5 mg strength and (b) (4) for 10 mg strength. The Pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D., e-mail dated 07-APR-08) informed that the degradant (b) (4) is qualified in preclinical studies. In response to the deficiencies (IR letter dated 08-APR-08) the proposed acceptance criteria for (b) (4) and for total degradation products have been revised for both strengths, consistent with batch analysis data and with additional primary stability results, now available through 24 months of storage. Revised acceptance criteria for (b) (4) are (b) (4) (initially proposed (b) (4)) and (b) (4) for 5 mg and 10 mg strengths, respectively. Strength specific acceptance criteria ensure a

Chemistry Assessment Section

tighter control of degradation product levels for a given strength as compared to harmonizing the specifications across the 5 mg and 10 mg tablets. The pharm tox reviewer indicated in her review and e-mail dated 07-MAY-08 that degradant (b) (4) is qualified at (b) (4) level. In addition, these criteria are in accordance with Decision Tree #2 in ICH guideline Q6A. Similarly acceptance criteria for the total degradation products are tightened and revised for both strengths as (b) (4) (initially proposed (b) (4) for 5 mg and 10 mg strengths, respectively. In addition, the acceptance limit for each unspecified individual impurity for the 5 mg strength has been revised to (b) (4) in accordance with ICH guideline Q3B identification threshold. The limit of (b) (4) has already been proposed for the 10 mg strength in original NDA 22-117 submission.

Control of drug product is evidenced by the low variability of release data of 46 batches of 5 mg asenapine maleate tablets and 24 batches of 10 mg asenapine maleate tablets. This is true for assay, impurities, uniformity of content, uniformity of mass and water content. Consistent and satisfactory results were also obtained for appearance, identification and microbial tests. Furthermore, it should be noted that the above batches represent manufacturing at discrete batch sizes between the (b) (4) scales (commercial batch size). The data, therefore, lead to the inference that drug product quality is consistent through the scale employed in the manufacturing process for asenapine maleate drug product.

Stability data of the long term, intermediate, and 5° C/ambient RH (12 months) and accelerated (6 months) storage conditions study for three registration batches of each tablet strength (5 mg and 10 mg tablets) manufactured (b) (4) packaged in the proposed container closure system (blisters) is provided. The samples were tested for appearance, assay, degradation products, disintegration, moisture, dissolution, and polymorphic characteristics. Analytical methods not proposed for the commercial drug product (diameter, dissolution, polymorph and microbial limits) are included in the study protocol for primary stability batches. The diameter, dissolution, polymorph and microbial limits were performed during release and stability but are not included in the specification. Diameter testing was performed using digimatic caliper. Dissolution was performed using USP dissolution apparatus 2 (paddle) at 50 rpm with 500 mL pH 4.5 acetate buffer medium. A validated (b) (4) spectroscopic test method was applied for the determination of polymorphic forms (b) (4) and amorphous material in asenapine maleate tablets. Microbial limits were performed according to USP/Ph.Eur. With respect to the stability indicating parameters, the drug product did not change significantly, with exception of a slight increase of an unspecified degradation product for the 5 and 10 mg tablets. The test results for the drug product remained within the shelf-life specifications after 12 months of storage at 25° C/60% RH and 30° C/65% RH and after 6 months of storage at 40° C/75% RH. The applicant provided statistical analysis of the stability data from the 30° C/75% RH storage condition for asenapine 5 mg and 10 mg tablets for the estimation of expiration date. Based on the results, the applicant claimed a shelf-life period of 2 years for asenapine maleate 5 and 10 mg tablets in blisters when stored at controlled room temperature conditions 15-30° C (59-86° F)].

In NDA amendment #0024 dated 30-APR-08, the applicant provided updated stability data and statistical analysis (30° C/75% RH storage condition) for asenapine 5 mg and 10 mg tablets and confirmed expiration date of 24 months initially granted during review #1 based on 18 months long term stability data provided in the original submission of the NDA.

Drug substance

According to Biopharmaceutics Classification System (BCS), asenapine maleate is classified as a BCS Class 2 compound (low solubility, high permeability). Asenapine maleate is a white to off-white powder with a solubility of 3.7 mg/mL in water. Asenapine maleate is a chiral compound with two chiral centers but is being developed as the racemate. (b) (4) polymorphs (b) (4)

Chemistry Assessment Section

(b) (4)

specifications for the each specified impurity (b) (4) each unspecified impurity, (b) (4), and sum of specified and unspecified impurities, (b) (4) were provided. In e-mail (dated 26-MAR-08) and in the NDA WRAP-UP meeting (dated 07-APR-2008), the pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) indicated that the data supporting qualification of impurity (b) (4) at the level (b) (4) was not acceptable and that additional information will be requested. However, in the WRAP-UP meeting, Dr. Barry Rosloff (Pharmtox Team Leader) stated that the limit for impurity (b) (4) is acceptable; unless the "requested" phase 4 studies (when done correctly) show a problem. If a problem is seen, then the limit for this impurity will need to be lowered. However, in pharmtox review dated 30-APR-08, it is stated to perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or asked to reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4). Residual Solvents, (b) (4)

Release data of drug substance batches used in clinical trials, primary drug product stability studies, and manufacturing of registration batches is provided: Five (5) non-clinical/clinical/stability batches (#s from C to K, manufactured January 1979-January 1994, Batch size range (b) (4) have been manufactured in the facilities of N. V. Organon, located in Kloosterstraat, The Netherlands, twenty (20) clinical/stability batches (#s from L to AT, manufactured November 1998-January 2005, Batch size range (b) (4) have been manufactured in the facilities of N. V. Organon, located in Vlijtseweg, The Netherlands, and four (4) commercial size clinical/stability batches (#s from AV to AY, manufactured April-May 2005, Batch size range (b) (4) have been manufactured in the facilities of N. V. Organon, located in Veersemeer, The Netherlands. No significant variations between the individual asenapine maleate batches manufactured via the commercial process have been observed. Asenapine maleate batches are consistent with respect to the analytical parameters tested.

Chemistry Assessment Section

Long term (18 month) and accelerated Stability data of four drug substance batches of asenapine maleate is provided. The container closure system existed of double bags placed in barrels. A long term (12 month) and accelerated study of two of these Asenapine maleate batches, using (b) (4) bags with antistatic agents has also been conducted. Finally, photostability and forced degradation studies on asenapine maleate are provided. Based on the results of these studies, storage conditions and a re-test period (b) (4) for asenapine maleate are proposed. (b) (4)

real time stability data for 4 commercial batches.

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

Saphris® (asenapine) Sublingual Tablets will be marketed into blisters only. Summary for all of the Asenapine maleate tablet stability studies performed by N.V. Organon Pharmaceuticals Inc., The Netherlands is provided. The to-be-marketed asenapine maleate tablets include two strengths, 5 mg and 10 mg. Asenapine maleate tablets are packed in (b) (4) aluminum blister packs. The pockets are debossed to indicate the tablet strength. (b) (4)

. The recommended dose for the treatment of schizophrenia is 5 mg BID and 10 mg BID for the treatment of bipolar disorder. The suitability of the container/closure system is demonstrated by the stability data under ICH conditions in stability section of this review. Letter of Authorization to refer DMF (b) (4) for container closure is for use in packaging the tablets in blisters is provided. Certificate of analysis of the packaging components and adequate information about packaging components and manufacturer were provided in the NDA submission. The certificate of analysis reflected the results of testing performed in accordance with the specifications and current methods. The blister packages were selected based on their ability to adequately protect the product throughout its shelf life. Overall, stability data concluded to support 24-month expiration dating period for drug product stored at controlled room temperature conditions 15-30° C (59-86° F)]. [See USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf live. From the CMC point of view NDA 22-117 for Saphris® (asenapine) Sublingual Tablets is recommended **APPROVAL**.

III. Administrative**A. Reviewer's Signature**

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name:	Chhagan G. Tele, Ph.D.
Branch Chief Name:	Ramesh Sood, Ph.D.
Project Manager Name:	Keith Kiedrow, Pharm.D.

C. CC Block

See DFS.

15 Page(s) has been Withheld in Full following this page as B4 (CCI/TS)

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

/s/

Chhagan Tele
3/5/2009 02:31:50 PM
CHEMIST

Ramesh Sood
3/5/2009 02:48:04 PM
CHEMIST

MEMO

NDA 22-117

OND Division: Division of Psychiatry Products
Applicant: Organon USA Inc.
Letter Date: 31-AUG-07
Stamp Date: 31-AUG-07
PDUFA Date: 30-JUN-08
Trademark: Sycrest®
Established Name: asenapine maleate
Dosage Form: Sublingual Tablets (5 mg, 10 mg)
Route of Administration: Oral
Indication: Schizophrenia & acute manic or mixed episodes associated with Bipolar Disorder I
Reviewer: Chhagan G. Tele, Ph.D.

(b) (4)

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

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

/s/

Chhagan Tele
6/20/2008 03:33:56 PM
CHEMIST

Ramesh Sood
6/20/2008 04:30:39 PM
CHEMIST

**Sycrest®
(asenapine)
Sublingual Tablets**

NDA 22-117

**Division Director Review
Chemistry, Manufacturing, and Controls**

Applicant: Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Indication: Treatment of schizophrenia and treatment of acute manic or mixed episodes
associated with Bipolar I Disorder

Presentation: Sycrest® (asenapine) Sublingual Tablets are available in two strengths as round, white to off-white fast dissolving sublingual tablets at **5 mg strength** (with “5” on one side) or **10 mg strength** (with “10” on one side) and packaged in blisters, 10 blisters per card, 6 cards per carton (Child-resistant packaging) or 10 cards per carton (Hospital Unit Dose).

EER Status: Acceptable – 11-MAR-2008

Consults: Pharm/Tox **Approvable** – 30-APR-2008
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency will not be requested.

Original Submission: 30-AUG-2007

Post-Approval Agreements: None

Background:

This application was chosen by the Division of Psychiatry Products to serve as the pilot for the *Good Review Management Principles and Practices (GRMPs) for PDUFA Products (April 2005)*.

Drug Substance:

The drug substance, asenapine maleate, is a small, synthetic, new molecular entity (NME) with an empirical formula of $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ and a molecular weight of 401.84 (free base: 285.8). Known chemically as (3aRS,12bRS)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2Z)-2-butenedioate (1:1), it is white to off-white powder that melts at about 139.9 °C. It is slightly soluble

in water (3.7 mg/mL), displaying a pH of 4.6, and freely soluble in methanol, ethanol, and acetone. The pKa of the protonated base is 8.6. The molecule has two chiral centers but is being developed as the racemate. (b) (4) polymorphs have been found: (b) (4) is the most stable form at ambient temperature as the drug substance; (b) (4) is the most stable at high temperature. In addition, (b) (4) pseudopolymorphs were observed.

The manufacture of asenapine maleate is a (b) (4) process proceeding from a (b) (4) to yield the final drug substance.

The structure of asenapine maleate was (b) (4)

The proposed release specification for asenapine maleate includes: appearance, color, visible impurities, identification by IR, identification by (b) (4) High Performance Liquid Chromatography ((b) (4)-HPLC), (b) (4)

(b) (4). The reference standard is manufactured using the (b) (4) manufacturing process and has been adequately tested and meeting more stringent specification. Impurity reference standards have likewise been synthesized and characterized.

Adequate stability data were provided to support a (b) (4) retest date for the bulk drug substance, stored at controlled room temperature, inside (b) (4) bags contained in a barrel.

The applicant proposed an acceptance criterion for the impurity (b) (4) in asenapine maleate drug substance at (b) (4). Pharmacology recommends qualification of the impurity at this level or reduce the specification of such to the ICH Q3A(R) qualification limit of (b) (4). Release data for the drug substance batches used in clinical studies (20 batches) and batches used in to-be-marketed drug product batches (4 commercial batches) showed that this impurity is present at not more than (b) (4).

Conclusion: Drug substance is **unacceptable**.

Drug Product:

Sycrest® (asenapine) Sublingual Tablets are available in two strengths as round, white to off-white fast dissolving sublingual tablets at 5 mg strength (with “5” on one side) or 10 mg strength (with “10” on one side) and packaged in blisters.

The drug product is manufactured by the following steps:

(b) (4)

The composition of the 5 mg strength tablet is asenapine maleate (b) (4) gelatin NF (b) (4) and mannitol USP (b) (4) to give a total tablet weight of (b) (4). The composition of the 10 mg strength tablet is asenapine maleate (b) (4) gelatin NF (b) (4) and mannitol USP (b) (4) to give a total tablet weight of 30.47 mg.

Specification of the drug product includes: appearance, identification by (b) (4)-HPLC, identification by UV, assay by (b) (4).

Asenapine maleate tablets are packaged in (b) (4) aluminum blister packs. The pockets are debossed to indicate the tablet strength. The asenapine maleate tablets will be packaged in blisters, 10 blisters per card, 6 cards per carton (Child-resistant packaging) or 10 cards per carton (Hospital Unit Dose).

Adequate stability data were provided to support the proposed expiration dating of 24 months at room temperature, 59°- 86°F (15°- 30°C) for the drug product packaged in (b) (4) aluminum blister packs.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

The applicant agreed to follow the stability of the first three packaged lots of different bulk batches of each strength of product for 36 months and submit the results to the Annual Report.

The applicant agreed to place at least one commercial production lot of the drug product per year on stability for each strength and package configuration following the approved stability protocol.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. These methods are routine and will not be submitted to FDA laboratories for validation.

Overall Conclusion:

From a CMC perspective, the application is recommended to be **Approvable**. At this time, CMC is unable to accept the release criterion for the impurity (b) (4) and thereby approve the drug substance specification.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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

/s/

Blair Fraser
5/23/2008 08:22:10 AM
CHEMIST

NDA 22-117

SYCREST[®] (asenapine) Sublingual Tablets

Organon USA Inc.

Chhagan G. Tele, Ph.D.

**Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment**

**Division of Psychiatry Products
Review of Chemistry, Manufacturing, and Controls**

Table of Contents

DIVISION OF PSYCHIATRY PRODUCTS	1
Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and drug substance(s)	6
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	11
III. Administrative	11
A. Reviewer's Signature	11
B. Endorsement Block	11
C. CC Block	11
Chemistry Assessment	11

Chemistry Review Data Sheet

1. NDA: 22-117
2. REVIEW #: 2
3. REVIEW DATE: May 07, 2008
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-AUG-2007
Amendment #0007: Postapproval Stability Protocol and Commitment, Responses to CMC Information Request, and Catagorical Exclusion	10-DEC-2007
Amendment #0008: Revised draft carton and container labeling, (b) (4)	21-DEC-2007
Amendment #0009: Information on the antistatic agent in (b) (4) bags used in DS package	21-DEC-2007
Amendment #0014: Describes the liding foil used in blister packaging missing in NDA	17-JAN-2008
Amendment #0015: Information on the exclusion of DS Manufacturing site: N.V. Organon, Vlijtseweg 130, 7317 AK Apeldoorn, The Netherlands	30-JAN-2008
Amendment #0017: Blister foil labeling for both 5 and 10 mg sublingual tablets that will be printed to support product launch	21-FEB-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #0024: Response to CMC comments, IR letter 08-APR-08	30-APR-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon USA Inc.
Address:	56 Livingston Ave., Roseland, NJ 07068
Representative:	June Bray, Vice President, Regulatory Affairs
Telephone:	(973) 422-7201

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sycrest® (the proposed tradename)
b) Non-Proprietary Name (USAN-2002): asenapine maleate
c) Code Name/# (ONDC only): Org 5222
d) Chem. Type/Submission Priority (ONDC only):
• Chem. Type: 1
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1); Sycrest® (asenapine) Sublingual Tablets (5 mg and 10 mg Strengths)

10. PHARMACOL. CATEGORY: For the treatment of Schizophrenia and treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

11. DOSAGE FORM: Tablets (sublingual)

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 SPOTS product – Form Completed
 X Not a SPOTS product

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

USAN Name (2002): asenapine maleate

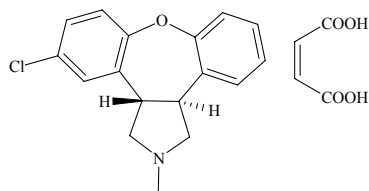
Non-Proprietary Name: (3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1)

Chemical Formula: C₁₇H₁₆ClNO.C₄H₄O₄

Molecular Weight: 401.84

CAS registry #: 85650-56-2; 65576-45-6 (asenapine)

Structure:



Asenapine maleate (Org 5222) contains two chiral centers. Asenapine maleate is a racemate.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	LOA 03-MAR-06

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51,641 (effective 30-SEP-1998) Sublingual Tablets	Commercial IND (Schizophrenia)
IND	70,329 (effective 03-AUG-2004) Sublingual Tablets	Commercial IND (Bipolar disorder)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation	11-MAR-08	Shawnte L. Adams (HFD-322)
Pharmtox	AE	30-APR-08	Elzbieta Chalecka-Franaszek, Ph.D.
Biopharm	Pending		Ron Kavanagh, Ph.D.
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	Pending		
EA	Acceptable, categorical exclusion granted as per information from Organon USA Inc. in this NDA	As per this review	Chhagan G. Tele, Ph.D. (ONDQA-Branch I)
Microbiology	N/A	N/A	N/A

NOTE: Division of Psychiatry Products has chosen this NDA to serve as the pilot for the new Good Review Management Principles and Practices (GRMPs) for PDUFA Products (Guidance for Review Staff and Industry: April 2005, Procedural).

The Chemistry Review for NDA 22-117

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant provided acceptable responses for the CMC deficiencies stated in the review #1 dated 11-APR-08 (see evaluation in the Chemistry Assessment section in this review). However, from the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE** due to pending resolution of the following outstanding pharmtox issue regarding impurity (b) (4) which will have impact as the setting of acceptance limit for the drug substance specification:

1. The applicant proposed acceptance criteria for impurity, (b) (4), in asenapine drug substance at (b) (4) which is above the ICH Q3A(R) qualification limit of (b) (4). The pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) stated in her review dated 30-APR-08 (pp. 4) that the applicant should perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4).

Release data for the drug substance batches used in clinical studies (20 batches) and batches used in to be marketed drug product batches (4 commercial batches) showed that process impurity (b) (4) is present at not more than (b) (4) level, which is well below ICH Q3A(R) qualification limit of 0.15% indicating that the applicant may be able to reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4).

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

None as per this review

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and drug substance(s)

General Product Information

Asenapine maleate (Company code: Org 5222) is a novel psychopharmacologic agent belonging to the group of dibenzoxepinopyrrolidine compounds. The active entity of asenapine maleate is asenapine. The proposed trade name for drug product is Sycrest®. Asenapine maleate exhibits high affinity and potency for blocking dopamine, serotonin, α -adrenergic and histamine receptors, and no appreciable activity at muscarinic and cholinergic receptors. The applicant claims that the rank order of receptor affinity for asenapine maleate reveals a unique human receptor binding signature, characterized by strong serotonergic properties, when compared to other antipsychotic drugs. Clinical development of asenapine maleate as an antipsychotic was started using a conventional oral formulation. However, this development was discontinued due to unexpected low bioavailability, caused by extensive first-pass metabolism in the liver and (probably) the gut. The bioavailability of orally taken asenapine maleate was more than 20 times lower than taken sublingually (respectively <2% versus 35%). Therefore, a sublingual formulation was developed to circumvent the hepato-gastro-intestinal first-pass metabolism. The applicant used (b) (4) technology to develop asenapine

Chemistry Assessment Section

(b) (4)

The recommended dose for the treatment of schizophrenia is 5 mg BID and 10 mg BID for the treatment of bipolar disorder.

Drug Product

The drug substance, asenapine maleate (New Molecular Entity) used for the manufacture of Sycrest Sublingual Tablets has been studied in commercial IND 51,641 (effective 30-SEP-1998) for the treatment of schizophrenia patients and IND 70,329 (effective 03-AUG-2004) for the treatment of bipolar disorder patients by Organon. For a period of time asenapine maleate was co-developed by both Organon and Pfizer (Organon no longer collaborating now with Pfizer). Asenapine maleate has not yet been approved for marketing in any country.

Asenapine maleate sublingual tablets will be available in two strengths, 5 mg and 10 mg. The 5 mg and 10 mg strengths are white to off-white circular tablets debossed with "5" or "10" on one side, respectively. Adequate information on components and composition of the proposed commercial drug product for unit dose formulation for two strengths is provided. Common excipients (gelatin and mannitol) of USP/NF/Ph. Eur or JP compendial grades are used to manufacture drug product. The manufacture of the drug product consists of (b) (4) proprietary manufacturing process: (b) (4)

Adequate information was provided for the manufacturing, release, and stability of the registration batches of the drug product from (b) (4) site. Information about controls of critical steps in the manufacture of registration batches of the Sycrest Tablets is provided. In-process tests (b) (4) were performed to maintain consistent manufacture of the drug product. The specifications for tablets included Description (Appearance: visual), Identification (UV, HPLC), Assay (HPLC), Impurities (HPLC), Disintegration, Content Uniformity (HPLC), and Water content. Validated analytical methods were provided in the submission. The asenapine maleate tablets will be packaged as: Child-resistant packaging-Box of 60: 6 blisters with 10 tablets (5 mg and 10 mg) and Hospital Unit Dose-Box of 100: 10 blisters with 10 tablets.

The release specification for assay of asenapine maleate tablets by HPLC is (b) (4) of label claim. A specific, stability indicating HPLC method and acceptance criteria have been developed for determination of identification, assay, and purity of asenapine maleate in Sycrest Tablets. The HPLC method is specific, with absence of interference from potential degradation products and impurities in the drug product. Assay specification for active ingredient is supported by values observed during release and stability studies of the drug product. This method has been validated with respect to specificity, linearity, working range, accuracy, method precision, limit of detection, and limit of quantitation. The purity acceptance criteria conformed to the limits of purity/degradation products observed during release and ongoing stability studies of Sycrest Tablets. Content Uniformity was performed using HPLC method. The proposed specification for Content Uniformity conforms to compendial USP <905> criteria and it is acceptable. Acceptance criteria for both strengths for the individual degradation product (b) (4), unspecified each individual impurities, and total

Chemistry Assessment Section

degradation products to the levels that are not consistent with data. The acceptable limits for impurities/degradation product should not be based on strength. The acceptance limit for unspecified each individual degradation product are different, (b) (4)

(b) (4) based on maximum daily dose of 20 mg/day. Similarly degradation product (b) (4) is the metabolite of asenapine in animals and humans with a structural alert for mutagenicity. The acceptance limit for this degradant is different for both strengths, (b) (4) for 5 mg strength and (b) (4) for 10 mg strength. The Pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D., e-mail dated 07-APR-08) informed that the degradant (b) (4) is qualified in preclinical studies. In response to the deficiencies (IR letter dated 08-APR-08) the proposed acceptance criteria for (b) (4) and for total degradation products have been revised for both strengths, consistent with batch analysis data and with additional primary stability results, now available through 24 months of storage. Revised acceptance criteria for (b) (4) are (b) (4) for 5 mg and 10 mg strengths, respectively. Strength specific acceptance criteria ensure a tighter control of degradation product levels for a given strength as compared to harmonizing the specifications across the 5 mg and 10 mg tablets. The pharm tox reviewer indicated in her review and e-mail dated 07-MAY-08 that degradant (b) (4) is qualified at (b) (4) level. In addition, these criteria are in accordance with Decision Tree #2 in ICH guideline Q6A. Similarly acceptance criteria for the total degradation products are tightened and revised for both strengths as (b) (4) for 5 mg and 10 mg strengths, respectively. In addition, the acceptance limit for each unspecified individual impurity for the 5 mg strength has been revised to (b) (4) in accordance with ICH guideline Q3B identification threshold. The limit of (b) (4) has already been proposed for the 10 mg strength in original NDA 22-117 submission.

Control of drug product is evidenced by the low variability of release data of 46 batches of 5 mg asenapine maleate tablets and 24 batches of 10 mg asenapine maleate tablets. This is true for assay, impurities, uniformity of content, uniformity of mass and water content. Consistent and satisfactory results were also obtained for appearance, identification and microbial tests. Furthermore, it should be noted that the above batches represent manufacturing at discrete batch sizes between the (b) (4) scales (commercial batch size). The data, therefore, lead to the inference that drug product quality is consistent through the scale employed in the manufacturing process for asenapine maleate drug product.

Stability data of the long term, intermediate, and 5° C/ambient RH (12 months) and accelerated (6 months) storage conditions study for three registration batches of each tablet strength (5 mg and 10 mg tablets) manufactured (b) (4) packaged in the proposed container closure system (blisters) is provided. The samples were tested for appearance, assay, degradation products, disintegration, moisture, dissolution, and polymorphic characteristics. Analytical methods not proposed for the commercial drug product (diameter, dissolution, polymorph and microbial limits) are included in the study protocol for primary stability batches. The diameter, dissolution, polymorph and microbial limits were performed during release and stability but are not included in the specification. Diameter testing was performed using digimatic caliper. Dissolution was performed using USP dissolution apparatus 2 (paddle) at 50 rpm with 500 mL pH 4.5 acetate buffer medium. A validated (b) (4) spectroscopic test method was applied for the determination of polymorphic forms (b) (4) and amorphous material in asenapine maleate tablets. Microbial limits were performed according to USP/Ph.Eur. With respect to the stability indicating parameters, the drug product did not change significantly, with exception of a slight increase of an unspecified degradation product for the 5 and 10 mg tablets. The test results for the drug product remained within the shelf-life specifications after 12 months of storage at 25° C/60% RH and 30° C/65% RH and after

Chemistry Assessment Section

6 months of storage at 40° C/75% RH. The applicant provided statistical analysis of the stability data from the 30° C/75% RH storage condition for asenapine 5 mg and 10 mg tablets for the estimation of expiration date. Based on the results, the applicant claimed a shelf-life period of 2 years for asenapine maleate 5 and 10 mg tablets in blisters when stored at controlled room temperature conditions 15-30° C (59-86° F)].

In NDA amendment #0024 dated 30-APR-08, the applicant provided updated stability data and statistical analysis (30° C/75% RH storage condition) for asenapine 5 mg and 10 mg tablets and confirmed expiration date of 24 months initially granted during review #1 based on 18 months long term stability data provided in the original submission of the NDA.

Drug substance

According to Biopharmaceutics Classification System (BCS), asenapine maleate is classified as a BCS Class 2 compound (low solubility, high permeability). Asenapine maleate is a white to off-white powder with a solubility of 3.7 mg/mL in water. Asenapine maleate is a chiral compound with two chiral centers but is being developed as the racemate. (b) (4) polymorphs (b) (4) have been found. (b) (4)

specifications for drug substance included Description (Appearance, Color, Visible impurities), Identification (b) (4)

specifications for the each specified impurity (b) (4), each unspecified impurity, (b) (4), and sum of specified and unspecified impurities, (b) (4) were provided. In e-mail (dated 26-MAR-08) and in the NDA WRAP-UP meeting (dated 07-APR-2008), the pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) indicated that the data supporting qualification of impurity (b) (4) at the level (b) (4) was not acceptable and that additional information will be requested. However, in the WRAP-UP meeting, Dr. Barry Rosloff (Pharmtox Team Leader) stated that the limit for impurity (b) (4) is acceptable; unless the "requested" phase 4 studies (when done correctly) show a problem. If a problem is seen, then the limit for this impurity will need to be lowered. However, in pharmtox review dated 30-APR-08, it is stated to perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or asked to

Chemistry Assessment Section

reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4). Residual Solvents, (b) (4)

Release data of drug substance batches used in clinical trials, primary drug product stability studies, and manufacturing of registration batches is provided: Five (5) non-clinical/clinical/stability batches (#s from C to K, manufactured January 1979-January 1994, Batch size range (b) (4) have been manufactured in the facilities of N. V. Organon, located in Kloosterstraat, The Netherlands, twenty (20) clinical/stability batches (#s from L to AT, manufactured November 1998-January 2005, Batch size range (b) (4) have been manufactured in the facilities of N. V. Organon, located in Vlijtseweg, The Netherlands, and four (4) commercial size clinical/stability batches (#s from AV to AY, manufactured April-May 2005, Batch size range (b) (4) have been manufactured in the facilities of N. V. Organon, located in Veersemeer, The Netherlands. No significant variations between the individual asenapine maleate batches manufactured via the commercial process have been observed. Asenapine maleate batches are consistent with respect to the analytical parameters tested.

Long term (18 month) and accelerated Stability data of four drug substance batches of asenapine maleate is provided. The container closure system existed of (b) (4) bags placed in barrels. A long term (12 month) and accelerated study of two of these Asenapine maleate batches, using (b) (4) bags with antistatic agents has also been conducted. Finally, photostability and forced degradation studies on asenapine maleate are provided. Based on the results of these studies, storage conditions and a re-test period (b) (4) for asenapine maleate are proposed. (b) (4)

real time stability data for 4 commercial batches.

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

Sycrest® (asenapine) Sublingual Tablets will be marketed into blisters only. Summary for all of the Asenapine maleate tablet stability studies performed by N.V. Organon Pharmaceuticals Inc., The Netherlands is provided. The to-be-marketed asenapine maleate tablets include two strengths, 5 mg and 10 mg. Asenapine maleate tablets are packed in (b) (4) aluminum blister packs. The pockets are debossed to indicate the tablet strength. (b) (4)

The recommended dose for the treatment of schizophrenia is 5 mg BID and 10 mg BID for the treatment of bipolar disorder. The suitability of the container/closure system is demonstrated by the stability data under ICH conditions in stability section of this review. Letter of Authorization to refer DMF (b) (4) for container closure is for use in packaging the tablets in blisters is provided. Certificate of analysis of the packaging components and adequate information about packaging components and manufacturer were provided in the NDA submission. The certificate of analysis reflected the results of testing performed in accordance with the specifications and current methods. The blister packages were selected based on their ability to adequately protect the product throughout its shelf life. Overall, stability data concluded to support 24-month expiration dating period for drug product stored at controlled room temperature conditions 15-30° C (59-86° F). [See USP Controlled Room Temperature].

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE** pending resolution of the following pharmtox issue regarding impurity (b) (4) which will have impact as the setting of acceptance limit for the drug substance specification. The applicant proposed acceptance criteria for impurity, (b) (4), in asenapine drug substance at (b) (4) which is above the ICH Q3A(R) qualification limit of (b) (4). The pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) stated in her review dated 30-APR-08 (pp. 4) that the applicant should perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4).

III. Administrative**A. Reviewer's Signature**

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name:	Chhagan G. Tele, Ph.D.
Branch Chief Name:	Ramesh Sood, Ph.D.
Project Manager Name:	Keith Kiedrow, Pharm.D.

C. CC Block

See DFS.

**8 Page(s) has been Withheld in Full following this page as
B4 (CCI/TS)**

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

/s/

Chhagan Tele
5/21/2008 01:01:21 PM
CHEMIST

Ramesh Sood
5/21/2008 04:45:29 PM
CHEMIST

NDA 22-117

SYCREST[®] (asenapine) Sublingual Tablets

Organon USA Inc.

Chhagan G. Tele, Ph.D.

**Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment**

**Division of Psychiatry Products
Review of Chemistry, Manufacturing, and Controls**

Table of Contents

DIVISION OF PSYCHIATRY PRODUCTS	1
Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and drug substance(s)	6
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative	10
A. Reviewer's Signature	10
B. Endorsement Block	10
C. CC Block	10
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	10
S DRUG SUBSTANCE	10
P DRUG PRODUCT	64
A APPENDICES	119
R REGIONAL INFORMATION	119
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	120
A. Labeling & Package Insert	120
B. Environmental Assessment Or Claim Of Categorical Exclusion	123
III. List Of Deficiencies To Be Communicated	124

Chemistry Review Data Sheet

1. NDA: 22-117
2. REVIEW #: 1
3. REVIEW DATE: April 07, 2008
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-AUG-2007
Amendment #0007: (Postapproval Stability Protocol and Commitment, Responses to CMC Information Request, and Catagorical Exclusion)	10-DEC-2007
Amendment #0008: (Revised draft carton and container labeling, (b) (4))	21-DEC-2007
Amendment #0009: (Information on the antistatic agent in (b) (4) bags used in DS package)	21-DEC-2007
Amendment #0014: (Describes the liding foil used in blister packaging missing in NDA)	17-JAN-2008
Amendment #0015: (Information on the exclusion of DS Manufacturing site: N.V. Organon, Vlijtseweg 130, 7317 AK Apeldoorn, The Netherlands)	30-JAN-2008
Amendment #0017: (Blister foil labeling for both 5 and 10 mg sublingual tablets that will be printed to support product launch)	21-FEB-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon USA Inc.
Address:	56 Livingston Ave., Roseland, NJ 07068
Representative:	June Bray, Vice President, Regulatory Affairs
Telephone:	(973) 422-7201

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sycrest® (the proposed tradename)
b) Non-Proprietary Name (USAN-2002): asenapine maleate
c) Code Name/# (ONDC only): Org 5222
d) Chem. Type/Submission Priority (ONDC only):
 • Chem. Type: 1
 • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1); Sycrest® (asenapine) Sublingual Tablets (5 mg and 10 mg Strengths)

10. PHARMACOL. CATEGORY: For the treatment of Schizophrenia and treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

11. DOSAGE FORM: Tablets (sublingual)

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 SPOTS product – Form Completed
 X Not a SPOTS product

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

USAN Name (2002): asenapine maleate

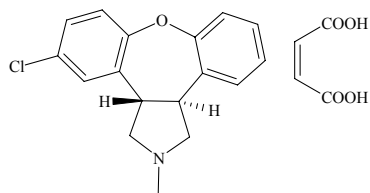
Non-Proprietary Name: (3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3-*b*,6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1)

Chemical Formula: C₁₇H₁₆ClNO.C₄H₄O₄

Molecular Weight: 401.84

CAS registry #: 85650-56-2; 65576-45-6 (asenapine)

Structure:



Asenapine maleate (Org 5222) contains two chiral centers. Asenapine maleate is a racemate.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	LOA 03-MAR-06

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51,641 (effective 30-SEP-1998) Sublingual Tablets	Commercial IND (Schizophrenia)
IND	70,329 (effective 03-AUG-2004) Sublingual Tablets	Commercial IND (Bipolar disorder)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending		Shawnte L. Adams (HFD-322)
Pharmtox	Pending		
Biopharm	Pending		Ron Kavanagh, Ph.D.
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	Pending		
EA	Acceptable, categorical exclusion granted as per information from Organon USA Inc. in this NDA	As per this review	Chhagan G. Tele, Ph.D. (ONDQA-Branch I)
Microbiology	N/A	N/A	N/A

NOTE: Division of Psychiatry Products has chosen this NDA to serve as the pilot for the new Good Review Management Principles and Practices (GRMPs) for PDUFA Products (Guidance for Review Staff and Industry: April 2005, Procedural).

The Chemistry Review for NDA 22-117

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE**. The outstanding issue is pending acceptable responses to the following CMC deficiencies.

1. The acceptable limits for impurities should not be based on strength. Reduce the acceptance criteria for both strengths for the degradation product (b) (4) and total degradation products to the levels that are more consistent with your data.
2. Revise unspecified each individual impurity limit for both strengths to no more than (b) (4) based on maximum daily dose of 20 mg/day.

Note: In e-mail (dated 26-MAR-08) and in the NDA WRAP-UP meeting (dated 07-APR-2008), the pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) indicated that the data supporting qualification of impurity (b) (4) at the level (b) (4) was not acceptable and that additional information will be requested. However, in the WRAP-UP meeting, Dr. Barry Rosloff (Pharmtox Team Leader) stated that the limit for impurity (b) (4) is acceptable; unless the "requested" phase 4 studies (when done correctly) show a problem. If a problem is seen, then the limit for this impurity will need to be lowered.

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

None as per this review

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and drug substance(s)

General Product Information

Asenapine maleate (Company code: Org 5222) is a novel psychopharmacologic agent belonging to the group of dibenzoxepinopyrrolidine compounds. The active entity of asenapine maleate is asenapine. The proposed trade name for drug product is Sycrest®. Asenapine maleate exhibits high affinity and potency for blocking dopamine, serotonin, α -adrenergic and histamine receptors, and no appreciable activity at muscarinic and cholinergic receptors. The applicant claims that the rank order of receptor affinity for asenapine maleate reveals a unique human receptor binding signature, characterized by strong serotonergic properties, when compared to other antipsychotic drugs. Clinical development of asenapine maleate as an antipsychotic was started using a conventional oral formulation. However, this development was discontinued due to unexpected low bioavailability, caused by extensive first-pass metabolism in the liver and (probably) the gut. The bioavailability of orally taken asenapine maleate was more than 20 times lower than taken sublingually (respectively <2% versus 35%). Therefore, a sublingual formulation was developed to circumvent the hepato-gastro-intestinal first-pass metabolism. The applicant used (b) (4) technology to develop asenapine maleate sublingual tablets. (b) (4)

Chemistry Assessment Section

(b) (4)

The recommended dose for the treatment of schizophrenia is 5 mg BID and 10 mg BID for the treatment of bipolar disorder.

Drug Product

The drug substance, asenapine maleate (New Molecular Entity) used for the manufacture of Sycrest Sublingual Tablets has been studied in commercial IND 51,641 (effective 30-SEP-1998) for the treatment of schizophrenia patients and IND 70,329 (effective 03-AUG-2004) for the treatment of bipolar disorder patients by Organon. For a period of time asenapine maleate was co-developed by both Organon and Pfizer (Organon no longer collaborating now with Pfizer). Asenapine maleate has not yet been approved for marketing in any country.

Asenapine maleate sublingual tablets will be available in two strengths, 5 mg and 10 mg. The 5 mg and 10 mg strengths are white to off-white circular tablets debossed with "5" or "10" on one side, respectively. Adequate information on components and composition of the proposed commercial drug product for unit dose formulation for two strengths is provided. Common excipients (gelatin and mannitol) of USP/NF/Ph. Eur or JP compendial grades are used to manufacture drug product. The manufacture of the drug product consists of (b) (4) proprietary manufacturing process: (b) (4)

Adequate information was provided for the manufacturing, release, and stability of the registration batches of the drug product from (b) (4) site. Information about controls of critical steps in the manufacture of registration batches of the Sycrest Tablets is provided. In-process tests (b) (4) were performed to maintain consistent manufacture of the drug product. The specifications for tablets included Description (Appearance: visual), Identification (UV, HPLC), Assay (HPLC), Impurities (HPLC), Disintegration, Content Uniformity (HPLC), and Water content. Validated analytical methods were provided in the submission. The asenapine maleate tablets will be packaged as: Child-resistant packaging-Box of 60: 6 blisters with 10 tablets (5 mg and 10 mg) and Hospital Unit Dose-Box of 100: 10 blisters with 10 tablets.

The release specification for assay of asenapine maleate tablets by HPLC is (b) (4) of label claim. A specific, stability indicating HPLC method and acceptance criteria have been developed for determination of identification, assay, and purity of asenapine maleate in Sycrest Tablets. The HPLC method is specific, with absence of interference from potential degradation products and impurities in the drug product. Assay specification for active ingredient is supported by values observed during release and stability studies of the drug product. This method has been validated with respect to specificity, linearity, working range, accuracy, method precision, limit of detection, and limit of quantitation. The purity acceptance criteria conformed to the limits of purity/degradation products observed during release and ongoing stability studies of Sycrest Tablets. Content Uniformity was performed using HPLC method. The proposed specification for Content Uniformity conforms to compendial USP <905> criteria and it is acceptable. Acceptance criteria for both strengths for the individual degradation product (b) (4), unspecified each individual impurities, and total degradation products to the levels that are not consistent with data. The acceptable limits for impurities/degradation product should not be based on strength. The acceptance limit for unspecified each individual degradation product are different, (b) (4)

based on maximum daily

Chemistry Assessment Section

dose of 20 mg/day. Similarly degradation product (b) (4) is the metabolite of asenapine in animals and humans with a structural alert for mutagenicity. The acceptance limit for this degradant is different for both strengths, (b) (4) for 5 mg strength and (b) (4) for 10 mg strength. The Pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D., e-mail dated 07-APR-08) informed that the degradant (b) (4) is qualified in preclinical studies.

Control of drug product is evidenced by the low variability of release data of 46 batches of 5 mg asenapine maleate tablets and 24 batches of 10 mg asenapine maleate tablets. This is true for assay, impurities, uniformity of content, uniformity of mass and water content. Consistent and satisfactory results were also obtained for appearance, identification and microbial tests. Furthermore, it should be noted that the above batches represent manufacturing at discrete batch sizes between the (b) (4) scales (commercial batch size). The data, therefore, lead to the inference that drug product quality is consistent through the scale employed in the manufacturing process for asenapine maleate drug product.

Stability data of the long term, intermediate, and 5° C/ambient RH (12 months) and accelerated (6 months) storage conditions study for three registration batches of each tablet strength (5 mg and 10 mg tablets) manufactured (b) (4) packaged in the proposed container closure system (blisters) is provided. The samples were tested for appearance, assay, degradation products, disintegration, moisture, dissolution, and polymorphic characteristics. Analytical methods not proposed for the commercial drug product (diameter, dissolution, polymorph and microbial limits) are included in the study protocol for primary stability batches. The diameter, dissolution, polymorph and microbial limits were performed during release and stability but are not included in the specification. Diameter testing was performed using digimatic caliper. Dissolution was performed using USP dissolution apparatus 2 (paddle) at 50 rpm with 500 mL pH 4.5 acetate buffer medium. A validated (b) (4) spectroscopic test method was applied for the determination of polymorphic forms (b) (4) and amorphous material in asenapine maleate tablets. Microbial limits were performed according to USP/Ph.Eur. With respect to the stability indicating parameters, the drug product did not change significantly, with exception of a slight increase of an unspecified degradation product for the 5 and 10 mg tablets. The test results for the drug product remained within the shelf-life specifications after 12 months of storage at 25° C/60% RH and 30° C/65% RH and after 6 months of storage at 40° C/75% RH. The applicant provided statistical analysis of the stability data from the 30° C/75% RH storage condition for asenapine 5 mg and 10 mg tablets for the estimation of expiration date. Based on the results, the applicant claimed a shelf-life period of 2 years for asenapine maleate 5 and 10 mg tablets in blisters when stored at controlled room temperature conditions 15-30° C (59-86° F)].

Drug substance

According to Biopharmaceutics Classification System (BCS), asenapine maleate is classified as a BCS Class 2 compound (low solubility, high permeability). Asenapine maleate is a white to off-white powder with a solubility of 3.7 mg/mL in water. Asenapine maleate is a chiral compound with two chiral centers but is being developed as the racemate. (b) (4)

Chemistry Assessment Section

(b) (4)

specifications for drug substance included Description (Appearance, Color, Visible impurities), Identification (b) (4)

(b) (4)

specifications for the each specified impurity (b) (4), each unspecified impurity, (b) (4) and sum of specified and unspecified impurities, (b) (4) were provided. In e-mail (dated 26-MAR-08) and in the NDA WRAP-UP meeting (dated 07-APR-2008), the pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) indicated that the data supporting qualification of impurity (b) (4) at the level (b) (4) was not acceptable and that additional information will be requested. However, in the WRAP-UP meeting, Dr. Barry Rosloff (Pharmtox Team Leader) stated that the limit for impurity (b) (4) is acceptable; unless the "requested" phase 4 studies (when done correctly) show a problem. If a problem is seen, then the limit for this impurity will need to be lowered. Residual Solvents, (b) (4)

Release data of drug substance batches used in clinical trials, primary drug product stability studies, and manufacturing of registration batches is provided: Five (5) non-clinical/clinical/stability batches (#s from C to K, manufactured January 1979-January 1994, Batch size range (b) (4)) have been manufactured in the facilities of N. V. Organon, located in Kloosterstraat, The Netherlands, twenty (20) clinical/stability batches (#s from L to AT, manufactured November 1998-January 2005, Batch size range (b) (4)) have been manufactured in the facilities of N. V. Organon, located in Vlijtseweg, The Netherlands, and four (4) commercial size clinical/stability batches (#s from AV to AY, manufactured April-May 2005, Batch size range (b) (4)) have been manufactured in the facilities of N. V. Organon, located in Veersemeer, The Netherlands. No significant variations between the individual asenapine maleate batches manufactured via the commercial process have been observed. Asenapine maleate batches are consistent with respect to the analytical parameters tested.

Long term (18 month) and accelerated Stability data of four drug substance batches of asenapine maleate is provided. The container closure system existed of (b) (4) bags placed in barrels. A long term (12 month) and accelerated study of two of these Asenapine maleate batches, using (b) (4) bags with antistatic agents has also been conducted. Finally, photostability and forced degradation studies on asenapine maleate are provided. Based on the results of these studies, storage conditions and a re-test period (b) (4) for asenapine maleate are proposed. (b) (4)

real time stability data for 4 commercial batches.

Chemistry Assessment Section

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

Sycrest® (asenapine) Sublingual Tablets will be marketed into blisters only. Summary for all of the Asenapine maleate tablet stability studies performed by N.V. Organon Pharmaceuticals Inc., The Netherlands is provided. The to-be-marketed asenapine maleate tablets include two strengths, 5 mg and 10 mg. Asenapine maleate tablets are packed in (b) (4) aluminum blister packs. The pockets are debossed to indicate the tablet strength. (b) (4)

(b) (4). The recommended dose for the treatment of schizophrenia is 5 mg BID and 10 mg BID for the treatment of bipolar disorder. The suitability of the container/closure system is demonstrated by the stability data under ICH conditions in stability section of this review. Letter of Authorization to refer DMF (b) (4) for container closure is for use in packaging the tablets in blisters is provided. Certificate of analysis of the packaging components and adequate information about packaging components and manufacturer were provided in the NDA submission. The certificate of analysis reflected the results of testing performed in accordance with the specifications and current methods. The blister packages were selected based on their ability to adequately protect the product throughout its shelf life. Overall, stability data concluded to support 24-month expiration dating period for drug product stored at controlled room temperature conditions 15-30° C (59-86° F). [See USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE** pending acceptable responses to the CMC deficiencies. This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR §25.31(a).

III. Administrative**A. Reviewer's Signature**

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name:	Chhagan G. Tele, Ph.D.
Branch Chief Name:	Ramesh Sood, Ph.D.
Project Manager Name:	Keith Kiedrow, Pharm.D.

C. CC Block

See DFS.

118 Page(s) has been Withheld in Full following this page as B4 (CCI/TS)

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

/s/

Chhagan Tele
4/11/2008 04:16:41 PM
CHEMIST

Ramesh Sood
4/11/2008 04:57:27 PM
CHEMIST