CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-117

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 22, 2008
To:	Thomas Laughren, M.D., Director Division of Psychiatric Products (DPP)
Thru:	Claudia Karwoski, Pharm.D., Acting Director Office of Surveillance and Epidemiology (OSE)/Division of Risk Management (DRISK)
From:	**OSE Sycrest RiskMAP Review Team** Scientific Lead Jeanine Best, MSN, RN, PNP, Senior Drug Risk Management Analyst, DRISK Daniel Bronstein, MPH, Regulatory Project Manager, OSE-IO Mary Dempsey, Risk Management Coordinator, DRISK Ida-Lina Diak, PharmD, Safety Evaluator, DAEA I Marilyn Pitts, PharmD, Safety Evaluator Team Leader, DAEA I
Subject:	Risk Minimization Action Plan
Drug Name(s):	Sycrest® (asenapine maleate) Sublingual Tablets
Application Type/Number:	NDA 22-117
Applicant/sponsor:	Organon
OSE RCM #:	2007-2009

1 INTRODUCTION

This memorandum follows a request from the Division of Psychiatric Products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Sycrest (asenapine maleate) Sublingual Tablets Risk Management Plan (RMP) submitted to FDA by Organon on August 30, 2007, as part of the original New Drug Application (NDA) 22-117.

Asenapine maleate is a novel psychotropic belonging to the group of dibenzoxepinopyrrolidine compounds and it exhibits a high affinity and potency for blocking dopamine, serotonin, α-adrenergic and histamine receptors, and no appreciable activity at muscarinic and cholinergic receptors. Sycrest was submitted for the indication of: "for the treatment of schizophrenia and for the treatment of acute manic or mixed episodes associated with Bipolar l Disorder."[1]

Sycrest will be available as a sublingual tablets containing 5 or 10 mg of asenapine maleate. Sublingual tablets were developed to circumvent the low bioavailability of oral tablets from extensive hepato-gastro-intestinal first pass metabolism.

2 MATERIAL REVIEWED

- Risk Management Plan for Sycrest, submitted with NDA 22-117, August 30, 2007

3 RESULTS OF REVIEW

3.1 SPONSOR SAFETY CONCERNS

Organon identified the following known and potential risks with asenapine maleate:

- Embyonic toxicity in animals
- Extrapyramidal symptoms (EPS)
- Neuroleptic Malignant Syndrome (NMS)
- Weight gain
- Somnolence and sedation
- Rhabdomyolisis
- Seizures
- Lipid profile changes
- Hyperprolactinemia
- Cardiovascular adverse events and ECG changes
- Suicidality
- Diabetes mellitus and hyperglycemia
- Liver related signs and symptoms
- Dysphagia
- Body temperature regulation
- Drug-drug interactions (fluvoxamine, paroxetine, and drugs predominately metabolized by CYP2D6)

Organon reports that these identified and potential risks are consistent and comparable with those of already approved atypical antipsychotic products. In addition, Organon reports that bioavailabity of the sublingual tablets decreases with food or water intake sooner than 10 minutes after asenapine administration.

[1] Cover Letter, Sycrest (asenapine maleate) Sublingual Tablets, NDA 22-117, August 30, 2007

3.2 POTENTIAL FOR MEDICATION ERRORS

Oral intake instead of sublingual use – OSE/DMEDP (Division of Medication Error Prevention) will provide a separate review encompassing the tradename review and potential medication errors.

3.3 PROPOSED RISK MINIMIZATION ACTIVITIES

Organon proposes routine risk minimization activities including labeling (Package Insert, carton labeling with patient instructions for use) and routine pharmacovigilance. No additional risk minimization activities are planned at this time.

4 DISCUSSION AND CONCLUSIONS

The Sponsor's submission does not constitute a formal Risk Minimization Action Plan (RiskMAP). In addition, DPP reported (in a mid-cycle NDA review meeting held February 1, 2008) that the identified and potential risks of asenapine are consistent and comparable with those of already approved atypical antipsychotic products. We agree with the Sponsor that routine risk minimization activities for Sycrest are adequate at this time based on the currently identified and potential risks of the product. No additional safety concerns have been identified at this time by either OSE or DPP that warrant consideration of a formal RiskMAP or additional risk minimization activities.

If DPP identifies additional safety concerns that warrant risk minimization activities above labeling and routine pharmacovigilance, or a formal RiskMAP, please re-consult OSE/Division of Risk Management.

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/s/

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2/22/2008 08:02:02 AM
DRUG SAFETY OFFICE REVIEWER

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2/25/2008 07:57:22 AM
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