New Drug Application
Memo to File - Clinical Pharmacology
Change in Recommendation

NDA:	22-117
Type of Submission:	Original NDA
Submission Date:	August 30, 2007
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)
Generic Name:	Asenapine Maleate
Formulation: **Strengths:**	Sublingual Tablets 5 mg, 10 mg
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)
Brand Name:	Sycrest®
Sponsor:	Organon / Schering-Plough
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Kavanagh, Ronald E

From: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 10:21 AM
To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
Subject: NDA 22-117 Asenapine Change in Recommendation

Mehul,

Per my 9 AM verbal notification I am changing my recommendation for asenapine (NDA 22-117) to nonapproval per FD&CA Sec. 505 d) 1) b; d) 2); d) 5; and c) 7.

As I was writing the labeling and trying to figure out how to discuss the drug interactions I realized that the information in the review indicates that asenapine causes pulmonary arterial hypertension and cardiac effects.

All of the cardiac and respiratory toxicities can potentially be explained by this, and appears to be the mechanism for the death 2 months after adding an antidepressant and may be an alternative mechanism for several deaths including the patient with Quincke's edema and the death of the neonate.

I'm also afraid that the nasal congestion and respiratory symptoms seen in many patients will be self mediated with OTC decongestants and will increase toxicity.

It appears that this toxicity is mediated by agonism at the 5HT2B receptor and is likely due to an active metabolite produced in the 11-hydroxylation cascade. Based on the sponsor's receptor binding information the metabolite involved might be the 11-O-Sulfate but it could be others.

The metabolic scheme, the mechanism, and the observed toxicities along with the study designs used by the sponsor in the drug-drug interaction studies, and the lack of many specific pieces of information in the submission as well as other things indicate that the sponsor knew about this toxicity and specifically tried to prevent our detecting it.

The potentially toxic metabolites are formed via CYPs 3A4 and 1A2, and based upon the use of this medication it will be used in subjects who have increased formation via these pathways and the long term toxicities may be subtle and not appreciated until well after marketing. Although based on the asenapine paroxetine drug interaction study at least ~60% of the patients taking this drug may be at risk and it is likely even higher in African Americans and children. (AA due to expression of 3A5 and children due to factors already mentioned.)

I simply do not believe there is anything we can do that would adequately educate physicians and patients to the risks and that with off-label use we will be looking at an epidemic of potentially lethal cardiac and pulmonary toxicities in children several years from now.

I believe that the pop PK findings in blacks are likely either erroneous or spurious and a dedicated PK study in appropriate subjects will demonstrate why pop PK studies are unreliable.

This only a brief summary and I intend to amend my review to include more details and request adequate time to fully document my concerns.

Ron

Tracking:

Recipient	Delivery	Read
Mehta, Mehul U	Delivered: 5/16/2008 10:21 AM	
Baweja, Raman K	Delivered: 5/16/2008 10:21 AM	Read: 5/16/2008 10:31 AM
Laughren, Thomas P	Delivered: 5/16/2008 10:21 AM	Read: 5/16/2008 10:28 AM
Temple, Robert	Delivered: 5/16/2008 10:21 AM	Deleted: 5/16/2008 4:35 PM

Kavanagh, Ronald E

From: Laughren, Thomas P
To: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 10:28 AM
Subject: Read: NDA 22-117 Asenapine Change in Recommendation

Your message

To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
Subject: NDA 22-117 Asenapine Change in Recommendation
Sent: 5/16/2008 10:21 AM

was read on 5/16/2008 10:28 AM.

Kavanagh, Ronald E

From: Temple, Robert
To: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 4:35 PM
Subject: Not read: NDA 22-117 Asenapine Change in Recommendation

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To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
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was deleted without being read on 5/16/2008 4:35 PM.

Kavanagh, Ronald E

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 4:55 PM
To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Ron,

Please go ahead with your plan to undertake further evaluation of this new safety issue that has just been identified. Please send me a brief e mail COB Wednesday, May 21st, describing your progress, whether more time is needed and if so, how much more and to evaluate what remaining information.

Mehul

Note: New Address

Mehul Mehta, Ph.D.
Director
Division of Clinical Pharmacology I
Office of Clinical Pharmacology
OTS, CDER, FDA
Building 51, Room 2178
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301)796-2140
fax (301)847-8712
mehul.mehta@fda.hhs.gov

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 1:37 PM
To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Ron,

I am trying to get in touch with Tom to discuss how much extra time can be made available and will let you know as soon as we are able to finalize it. In the meanwhile, please complete your labeling comments by the end of today to the extent you can, based on what you know so far.

Mehul

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Ron

Kavanagh, Ronald E

From: Kavanagh, Ronald E
Sent: Tuesday, May 20, 2008 4:54 PM
To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Mehul,

As you are aware from previous discussions I do not believe it is possible to write labeling with the present lack of information, and I was excused from writing labeling.

Today Ray told me that he is writing labeling. Since this must be based on the current version of my review prior to any amendment that you indicated I have until COB tomorrow to write, I must indicate my objection.

Ron

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

/s/

Ron Kavanagh
5/20/2008 05:10:26 PM
BIOPHARMACEUTICS