New Drug: Agomelatine

(Agomelatine Tablets 25mg has been approved by the CDSCO for marketing in India on 10.09.2012 for the treatment of major depression in adult patients aged 18 – 65 years only with normal liver functions- Editor)

Valdoxan (Servier)
25 mg tablets
Approved indication: major depression

Australian Medicines Handbook section 18.1

Agomelatine is a synthetic analogue of melatonin. The manufacturers claim that as well as agonising melatonin, it also antagonises the serotonin 5HT_{2C} receptors.

Numerous placebo-controlled trials have assessed the efficacy of agomelatine for major depression.\textsuperscript{1–5} The primary endpoint in these studies was based on the 17-item Hamilton rating scale for depression. At baseline, average scores were around 27 out of a possible 52. After 6–8 weeks, both agomelatine (25 or 50 mg) and placebo had reduced the scores (to between 12.8 and 19.6). Although agomelatine reduced the score significantly more than placebo in most comparisons, the mean difference between agomelatine and the placebo was never more than a few points. For example in a trial of 503 randomised patients, mean scores were reduced to 17.1 with placebo and to 15.0 and 15.9 with agomelatine 25 mg and 50 mg.\textsuperscript{5}

Agomelatine has also been compared with other antidepressants. A comparative trial with sertraline favoured agomelatine after six weeks, however, the difference in mean scores (Hamilton rating scale) between treatments was only 1.68.\textsuperscript{6} Agomelatine has also been compared to fluoxetine and paroxetine. However, superiority of the active treatments over placebo was not consistently shown and most of these studies have not been published.

The ability of agomelatine to prevent relapse of major depression has also been investigated in a 24-week trial of
patients who had already responded to 8–10 weeks of agomelatine treatment. Relapse rates were significantly lower for patients who continued agomelatine (after 8–10 weeks) compared to those who switched to placebo (20.6% vs 41.4%). However in a similar but unpublished study, relapse rates for agomelatine and placebo were not significantly different (25.9% vs 23.5%).

After oral administration, agomelatine is rapidly absorbed with peak plasma concentrations reached within 1–2 hours. Bioavailability is low and varies considerably between individuals. It is increased by oral contraceptives and female gender and decreased by smoking. Agomelatine is rapidly metabolised by the cytochrome P450 isoenzyme CYP1A2, and to a lesser extent by CYP2C9 and CYP2C19. The inactive metabolites are mainly eliminated in the urine. Potent inhibitors of CYP1A2, such as fluvoxamine or ciprofloxacin, are contraindicated with agomelatine and caution is urged if patients are taking a moderate inhibitor such as propranolol.

Over 3900 patients took agomelatine in the depression trials. The most common adverse effects were headache (14.1%), nausea (7.7%), dizziness (5.5%), dry mouth (3.5%), diarrhoea (3.1%), somnolence (2.9%), fatigue (2.6%), abdominal pain (2.4%) and insomnia (2.4%). These were mostly mild to moderate. There were four deaths out of 3956 patients who took agomelatine and one out of 826 patients who took placebo - these were all due to suicide. There were more suicide attempts with agomelatine than with placebo (0.6% vs 0.4%).

Increases in liver enzymes (more than three times the upper limit of normal range) occurred in around 1% of people taking agomelatine. This effect seemed to be dose-related. Serious hepatic reactions included hepatitis and a transaminase elevation more than 10 times the upper limit of the normal range. Agomelatine should not be given to people with cirrhosis or active liver disease. Liver function tests should be performed before a patient starts treatment and at regular intervals during treatment. Consuming alcohol with agomelatine is not advisable.

Caution is urged in patients with impaired renal function and those aged 65 or over. Agomelatine should not be used in elderly patients with Alzheimer's disease.

Although agomelatine reduces symptoms of depression on the Hamilton rating scale, its effect seems to be only marginally better than placebo, if at all. This questionable efficacy coupled with the potential risk of adverse hepatic reactions suggests that doctors are probably better continuing with the more established antidepressants.

References:

3. Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2c antagonistic properties, in major depressive
disorder. Int J Neuropsychopharmacol
and to a lesser extent by CYP2C9 and
A, Caputo A, Post A. Efficacy and
safety of agomelatine in the treatment
of major depressive disorder. J Clin
Psychopharmacol 2010;30:135-44.
5. Stahl SM, Fava M, Trivedi MH, Caputo
A, Shah A, Post A. Agomelatine in the
treatment of major depressive
disorder: an 8-week, multicenter,
randomized, placebo-controlled trial. J
6. Kasper S, Hajak G, Wulff K,
Hoogendijk WJG, Montejo AL,
Smeraldi E, et al. Efficacy of the novel
antidepressant agomelatine on the
circadian rest-activity cycle and
depressive and anxiety symptoms in
patients with major depressive
disorder: a randomized, double-blind
comparison with sertraline. J Clin
7. Goodwin GM, Emsley R, Rembry S,
Rouillon F; Agomelatine Study Group.
Agomelatine prevents relapse in
patients with major depressive
disorder without evidence of a
discontinuation syndrome: a 24-week
randomized, double-blind, placebo-
controlled trial. J Clin Psychiatry
2009;70:1128-37.

Ref. Aust Prescr 2010; 33:160-3

New rules on importing active
pharmaceutical ingredients into the
European Union

The European Union (EU) has reformed
the rules for importing into the EU active
substances for medicinal products for
human use.
As of 2 January 2013, all imported active
substances must have been
manufactured in compliance with
standards of good manufacturing
practices (GMP) at least equivalent to the
GMP of the EU. The manufacturing
standards in the EU for active substances
are those of the ‘International Conference
for Harmonisation’ – ICH Q7.
As of 2 July 2013, this compliance must
be confirmed in writing by the competent
authority of the exporting country. This
document must also confirm that the
plant where the active substance was
manufactured is subject to control and
enforcement of good manufacturing
practices at least equivalent to that in the
EU.

More information is available here:
http://ec.europa.eu/health/files/docu
ments/active_pharmaceutical_ingredie
nts_leaflet_en.pdf

NHRC committee to frame
guidelines for drug trials

The National Human Rights Commission
(NHRC) on Friday, 26th October 2012 said
it has constituted an expert committee to
frame guidelines for clinical drug trials,
following complaints alleging unethical
clinical drug trials in the country.

“NHRC has constituted an expert
committee for framing of some guidelines
for clinical trials of drugs in the country,”
a statement from the commission said.

“The commission has also decided to
intervene in the case relating to the
clinical trials of drugs pending before the
Supreme Court,” the statement said.

The committee comprises of Dr D C
Doval, director, research and medical
oncology, Rajiv Gandhi Cancer Institute
and Research Centre, New Delhi; Dr
Vivekanand Jha, professor, department of
nephrology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh; Dr B N Dhawan, former director, Central Drug Research Institute (CDRI), Lucknow and chairman, institutional ethics committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow; Dr Subhash Yadav, additional professor, department of endocrinology and member secretary, institutional ethics committee, SGPGI, Lucknow; and Dr Nilima Kshirsagar, national chair in clinical pharmacology, Indian Council of Medical Research (ICMR). The NHRC will coordinate the meetings of the committee, the statement said.

“The decision was taken in connection with some cases it registered suo motu on the basis of media reports alleging unethical clinical drug trials in the country. Commission had also received some complaints on the issue,” the NHRC statement added.

Source: IANS

**Feds fine Boehringer Ingelheim $95M in improper marketing case**

Germany’s Boehringer Ingelheim Pharmaceuticals has agreed to pay $95 million to resolve allegations relating to the improper promotion of the stroke-prevention drug Aggrenox, COPD drugs Atrovent and Combivent, and the hypertension drug Micardis, the Justice Department said yesterday.


**Meningitis outbreak widens to 323 cases in 18 States**

The AP reports that “323 Americans” have now been infected with meningitis and 24 people, who “received contaminated epidural steroid injections made by the New England Compounding Center,” have died, according to the Centers for Disease Control and Prevention’s latest update. Meanwhile, the Food and Drug Administration “confirmed the same fungus found in at least 40 people sickened with fungal meningitis was also discovered in more than 50 unopened vials from one of the recalled lots of preservative-free methylprednisolone acetate injections” from the NECC’s facility in Framingham, Massachusetts.

Reuters reports that one of the 11 new cases was a patient in South Carolina, making it the 18th state affected by the outbreak.

On its website, NPR noted the update in segments of “Talk of The Nation” in which host Neal Conan discussed the safety issues at the NECC with NPR Health Science Correspondent Richard Knox in Washington.

**Forthcoming Event:**

**State Round of National Elocution Competition (West Bengal)**

**Date:** 3rd November 2012.

**Time:** 3.00 p.m

**Venue:** Indian Pharmaceutical Association, Bengal Branch

22 B Panchanontola Road

Kolkata-70084

**Topic:** “Pharma Education – Present Scenario & Future Prospects”

**Time:** 8+2 Minutes

Contestants are advised to report at 2.30 pm at the venue on 3rd November 2012.

For Details contact:

**Dr. Subhash C. Mandal**

State Co-ordinator-NEC 2012

Mob. 9830136291