

**BEFORE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI**

THE PATENTS ACT 1970
(Section 15)

In the matter of application No.
1003/DEL/2006 dated 12th July 2004 filed by
M/S Les Laboratoires Servier, of 12, place de La
Defense, 92415 Courbevoie Cedex, France

Hearing held on 05th March 2009 at 11:30 A.M.

Present:

1. Sh. Shukadev Khurajam ---- --- Agent representing the applicant
2. Dr. Rohit Rathore ----- Examiner of Patents & Designs

O R D E R

M/S Les Laboratoires Servier, of 12, place de La Defense, 92415 Courbevoie Cedex, France through their patent attorneys M/S Remfry & Sagar filed a patent application No. 1003/DEL/2006 on 18th April 2006 for their invention related to “Use of agomelatine in obtaining medicaments intended for the treatment of bipolar disorders”.

2. The first examination report (FER) thereof was issued on 8th February 2008 vide this office letter No. 1003/DEL/2006/9735. The examination report *inter-alia* contained the objections relating to lack of novelty and inventive step u/s 2(1)(j) of the Patents Act 1970 in view of patent documents WO2005/063297 and Non Patent Literature (NPL) namely Chilman Blair K et al., vol. 2, no. 1, January 2003, pages, 7-13 & Graul A I, vol. 28, no. 11, 2003, pages 1103-1144 and also the subject matter of claims is not patentable within the provisions of clause (d) and (e) of Section 3 of Patents Act 1970 as amended in 2005.

3. The agents for the applicant responded to the objections contained in First Examination Report on 07th August 2008 and resubmitted the documents along with amended claims. The revised claims were examined and case was discussed with the agent for the applicant who further filed a detailed clinical study on 2nd February 2009 for establishing the effects shown by the claimed associations (combination) containing agomelatine and optionally a

thymoregulatory agent for the treatment of bipolar disorders and to corresponding pharmaceutical composition. The agent claimed that study shows that the results obtained with the combinations are much better than the base line observed with the thymoregulatory agent. Further examination report sent to the applicant on 5th February 2009 and both the objections stated above were retained along with a new citation of patent document EP1564202. The agent for the applicant refiled the documents on 9th February 2009 and submitted following observations:

(a) EP 1564202

As regards the new prior art EP 1564202 cited by the learned Examiner, it is submitted that the said prior art is not very pertinent as it discloses a new process for the synthesis of agomelatine and the access to this new crystalline form with this new process. The new crystalline form can be used "*for the treatment of sleep disorders, stress, anxiety, seasonal affective disorders or severe depression, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease.* As a consequence, cited document EP1564202 discloses crystalline form II of agomelatine for its antidepressant properties, but not for bipolar disorders: bipolar disorders are disorders perfectly well-characterized in the official classification of DSM-IV (Manuel Diagnostique et Statistique des Troubles Mentaux, 4e edition, American Psychiatric Association) for which there is till now no existing drug with real efficacy. It is not disclosed nor suggested in EP1564202 the use of agomelatine for bipolar disorders, so that our present invention is new and inventive over this cited prior art. It is submitted that the documents pertinent to consider are D1 (ChilmanBlair K. et al., Drugs of the Future, 28(1), 2003, 7-13) and D2 (Graul A.I., Drugs of the Future, 28 (11), 2003, 1103-1144).

(a) Chilman-Blair K. et al., Drugs of the future, 28 (1), 2003, 7-13

(D1) :

As regards D1 it is submitted that this paper is a general review concerning agomelatine and its pharmacological properties. These properties are supported with clinical studies showing the antidepressant effect of agomelatine in patients suffering from major depression. A first clinical study is described on 28 patients suffering

from major depression (see page 11 in Table II first part) and demonstrates the efficacy of agomelatine in that pathology. The second one (see page 11 in Table II second part), implying much more patients (711) is intended to show the efficacy of agomelatine in the treatment **of major** depression compared to paroxetine (see on page 11 line first column second paragraph). This study is referenced to number 38 of the article as "Loo et al., Determination of the dose of agomelatine, a melatonergic agonist and selective 5-HT_{2c} antagonist, in the treatment of major depressive disorder." This study is described implying 711 patients among who 698 are diagnosed major depressed people. Only 13 patients are diagnosed as patients suffering from bipolar II disorder. For this pathology, well defined in the DSM-IV classification and for which no real treatment exists, antidepressants are commonly tested. The aim of the described clinical study wasn't to find a new treatment for bipolar II disorders but to prove the efficacy of agomelatine compared to paroxetine in the major depression: the number of included patients in each group was *an* average of 140 (see Table 11 line 2), which is to say that the representation of bipolar patients was marginal and not significant. Taking these arguments into account, it can't be considered that the present invention claiming the use of agomelatine for the treatment of bipolar patients was anticipated in the cited prior art D1.

Graul A. 1., Drugs of the future, 28(11), 2003, 1103-1144 (D2)

As regards D2 which was published at the same time with the same general knowledge on the matter, it is clear from the Table on page 1104 which makes an Update of the drugs used in psychiatric disorders, that agomelatine is used for the treatment of depression (major). No reference is done to bipolar disorders. Moving to the part "Bipolar disorders" on page 1111 to 1113 of the reference, table X refers to antidepressant compounds for the treatment of bipolar disorders and no mention is done concerning agomelatine.

In view of said submissions the agent for the applicant resisted and reiterated that the claimed invention is novel and inventive over the cited prior art documents.

4. Regarding the objection of section 3(d), the agent submitted that the claims on file do not relate to a new form or a new use of a known compound, rather, the same relate to a novel and synergistic association/ pharmaceutical composition and regarding the objection of section 3(e) & 3(i) they stated that the amended claims do not fall within the ambit of section 3(e) and Sec. 3(i). The case discussed with the agent for the applicant, Ms. Payal Kalra who asked for an

opportunity of being heard in the matter and subsequently a hearing letter along with following objections issued on 18.02.09 :

- (i) Claims 1-8 fall within the scope of such clause (d) and (e) of section 3 and claims 3-7 appears to fall within the scope of such clause (i) of section 3.
- (ii) Subject matter of claims lack novelty and inventive step in view of cited documents (a) Chilman Blair K et al, vol. 28, no.1, January 2003, pages 7-13 (b) Graul A I, vol.28, no.11, 2003, pages 1103-1144 & (iii) EP1564202
- (iii) Each set of claims 1-2 and 3-8 relate to independent inventions.
- (iv) Claim-1 do not sufficiently define the invention w.r.t. to the nature and amount of components present in composition claimed. Claims 3-6 not clear w.r.t. to the term associations.

5. The agent during hearing submitted seven amended claims out of which they deleted the claims no. 2-7. Now only claim-1 remains in the file which is as follows:

“Pharmaceutical compositions for the treatment of bipolar disorders. Of type I comprising agomelatine or one of its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, on its own or in combination with one or more pharmaceutically acceptable excipients, and a thymoregulatory agent.”

In their written submission submitted during hearing on 5th March 2009 the agent for the applicant stated that

- (i) With reference to section 3(d) they submit the same observations as filed earlier.
- (ii) With reference to section 3(e) they submit that the combination of agomelatine and thermoregulatory agent in a pharmaceutical composition is synergistic in nature, and the same is established by the clinic trail study filed earlier. They further submitted that the only way to prove the benefit of the compound is to compare the results obtained with the combination and with the thymoregulatory agent alone given at the highest doses. The fact that the test to prove a synergy between the two components, agomelatine and thermoregulatory agent, is unconceivable in patients suffering from bipolar disorder type I because it is not ethical to stop the thermoregulatory therapy considering the high risk that would be taken beside their life. As regards the specific amount of the active ingredients in the composition, the same is clear to a man skilled in the art that the dosage depends on and varies from a patient to another, and needs to be adapted in each case.

(iii) With regard to novelty and inventive step along with the earlier filed submission it was added that from the Chilman-Blair K. et al., Drugs of the future, 28 (1),2003,7-13 (D1) only conclusion that can be drawn is that agomelatine is efficient in the treatment of major depressive disorder and that 25 mg is the target dose. At the most the treatment of the major depressive episode in bipolar disorder of type II could be envisaged and it cannot be anticipated that a compound able to treat the depressive episode will definitely be a treatment for the bipolar disorder of type II. Also the claims have been restricted to the use of agomelatine in the treatment of bipolar disorder of type I.

6. I have examined the complete specification and the submissions filed. On perusal of these, it is found that in the description, there is no substantial support of the pharmaceutical composition as claimed in the claims obviously for the reason that the applicant wanted to claim the use of agomelatine and its hydrate,etc for treatment of biopolar disorder of type-I as agomelatine and its hydrate,etc are already know for the treatment of biopolar disorder of type-II. The alleged pharmaceutical composition as given on page 5 is already disclosed in prior art document namely EP1564202 (example-5) and therefore there is no novelty in the composition itself. Further the use of agomelatine and its hydrate,etc for treatment of biopolar disorder of type-I which is already know for type II is the case of mere use of known substance unless it results in the enhancement of its known efficacy. The clinical study provided on page 6 of the specification as well as in the submission, first of all nowhere talks about the percentage/ ratio of constituents of the claimed composition which leads to the conclusion that the alleged composition is mere admixture. Secondly it only provides result on the basis of dosage of aglomelatine and lithium or valpromide administered rather than a dosages of composition containing both in a certain quantities in order to prove the efficacy of the composition itself as well as synergism. Therefore in order to prove such efficacy and synergism the applicant must give comparative data with respect to the prior art, and claimed composition while claiming the improved properties of a composition. Even if it is presumed that the alleged composition is novel due to presence of thymoregulatory agent such as lithium or valpromide, it lacks inventive step due to absence of comparative data for its enhance efficacy ,synergism and lack of support of composition in the absence of any ratio or percentage of these ingredients in the description.

Having considered all the facts, submission made by the agent for the applicant during the hearing and as well as all the documents on record and also in view of my above findings, I hereby refuse this application to proceed further for grant of patent due to lack of inventive step, not patentable u/s 3(d) and 3(e) in accordance with the provisions of the Patents Act 1970.

Dated, the 13 day of May, 2009.

(Dr. K.S. Kardam)
Deputy Controller of Patents & Designs

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