HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 November 2009

VALDOXAN 25mg film-coated tablets
Pack of 28 tablets (CIP: 394 330-5)
Pack of 100 tablets (CIP: 575 145-5)

Applicant: SERVIER

agomelatine

ATC classification: N06AX22

List I

MA date: February 19, 2009
Centralised procedure – rapporteur: Norway

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance (packs of 28) and on the list of medicines approved for use by hospitals and various public services (packs of 28 and 100).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

agomelatine

1.2. Background

New class of antidepressant: melatonin receptor agonists and serotonin $5HT_{2c}$ receptor subtype antagonist.

1.3. Indication

“Treatment of major depressive episodes (i.e. characteristic symptoms) in adults”

1.4. Dosage

The recommended dose is 25 mg once daily taken orally at bedtime.
After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets taken together at bedtime.
Liver function tests should be performed in all patients : at initiation of treatment, and then periodically after around six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated .
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.
Valdoxan tablets may be taken with or without food.

Children and adolescents :
Valdoxan is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy.

Elderly patients:
Efficacy has not been clearly demonstrated in the elderly (≥ 65 years). Only limited clinical data is available on the use of Valdoxan in elderly patients ≥ 65 years old with major depressive episodes. Therefore, caution should be exercised when prescribing Valdoxan to these patients.

Patients with renal impairment:
No relevant modification in agomelatine pharmacokinetic parameters in patients with severe renal impairment has been observed. However, only limited clinical data on the use of Valdoxan in depressed patients with severe or moderate renal impairment with major depressive episodes is available. Therefore, caution should be exercised when prescribing Valdoxan to these patients.

Patients with hepatic impairment:
Valdoxan is contraindicated in patients with hepatic impairment

Treatment discontinuation:
No dosage tapering is needed on treatment discontinuation.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N	Central nervous system
N06	Psychoanaleptics
N06A	Antidepressants
N06AX	Other antidepressants
N06AX22	Agomelatine

2.2. Medicines in the same therapeutic category

This is the first melatonin receptor agonist and serotonin $5HT_{2c}$ receptor subtype antagonist antidepressant.

2.3. Medicines with a similar therapeutic aim

All other antidepressants.

3 ANALYSIS OF AVAILABLE DATA

The clinical studies provided in the application are:

- 5 phase III placebo-controlled studies evaluating the short term antidepressant effect
- 1 placebo-controlled dose-determining study evaluating the short term antidepressant effect
- 2 placebo-controlled studies evaluating the prevention of depression relapses after 6 months
- 3 short term active comparator-controlled studies
- 4 safety studies

For the majority of these studies, the antidepressive efficacy of agomelatine was evaluated using the approved HAMD17 criterion[1].

3.1. Efficacy

3.1.1. Short term placebo-controlled clinical studies

The fixed dose studies were mostly conducted using the 25 mg dosage, while the flexible dose studies used higher doses.

3.1.1.1. Short term placebo-controlled studies using flexible doses (25 to 50 mg) of agomelatine (CL3-042[2] and CL3-043[3])

These were 2 randomised, double-blind, placebo-controlled phase III studies.

---

[1] Hamilton Rating Scale for Depression - 17 items (scored 0 to 53).
Hamilton M. Development of a rating scale for primary depressive illness. Br J Social Clin Psychology 1967;6:278-96.

[2] Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. Int J Neuropsychopharmacol 2007;10:661-73

[3] Kennedy SH; Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur Neuropsychopharmacol 2006; 16:93-100

The treatment duration was 6 weeks, followed by an optional period of 46 weeks' treatment.

Patients included had to be aged 18 to 65 and suffer from a major depressive syndrome according to DSM-IV criteria. The HAMD17 scale score had to be at least 22. The patients were treated as outpatients in the CL3-043 study and as outpatients or inpatients in the CL3-042 study.

The dosage of agomelatine was flexible between 25 mg and 50 mg: 25 mg once daily at the start of the study, which could, in the absence of a response, be doubled to 25 mg twice daily after 2 weeks.

The primary endpoint was the change in the HAMD17 score after 6 weeks of treatment. One secondary analysis was the percentage of responsive patients(reduction in the HAM-D17 total score at inclusion $\geq$ 50%).

Results:
Randomised patients: 238 in study CL3-042 and 212 in study CL3-043.
In study CL3-042, the dose was increased after 2 weeks in 25% of agomelatine patients and in 45% of placebo patients.
In study CL3-043, the dose was increased after 2 weeks in 34% of agomelatine patients and in 36% of placebo patients.

Table 1: HAMD17 score for placebo-controlled agomelatine studies at flexible doses of 25 mg-50 mg

Study Treatment	Number of patients	Mean baseline HAMD17 score	Mean HAMD17 score at week 6*	Difference between groups**	95%CI	p
CL3-042 agomelatine placebo	 116 119	 27.4 27.2	 13.9 17.0	3.44	1.63 – 5.26	<0.001
CL3-043 agomelatine placebo	 106 105	 26.5 26.7	 14.1 16.5	2.30	0.28 – 4.31	0.026

* LOCF (last observation carry-forward)
** results adjusted to centre and baseline score.

The efficacy of agomelatine was greater than that of the placebo in both studies on moderate to severe depressive patients at a flexible dose of 25-50 mg. The improvement in the HAMD17 depression score observed with agomelatine compared to placebo was 3.44 points in study CL3-042 ($p<0.001$) and 2.30 ($p=0.026$) in study CL3-043.

The percentage of responsive patients was 54.3% with agomelatine compared to 35.3% with the placebo in study CL3-042 ($p=0.003$) and 49.1% with agomelatine compared to 34.3% with the placebo in study CL3-043 ($p=0.03$).

3.1.1.2. Short term placebo-controlled and active comparator-controlled studies using fixed doses (25 mg) (CL3-022, CL3-023, CL3-024 and CL3-014[4])

These were one phase II and 3 phase III randomised double-blind placebo-controlled studies with an active comparator to verify the trial's sensitivity.

Patients included had to be aged 18 to 65 and suffer from a major depressive syndrome according to DSM-IV criteria. The HAMD17 scale score had to be at least 22 (moderate to severe depression).

The patients were given a fixed dose:

- of 25 mg of agomelatine once daily in studies CL3-022 and CL3-023,
- of 25 mg or 50 mg depending on the group in study CL3-024,
- of 1 mg, 5 mg or 25 mg in the dose study CL3-014.

The study duration was 6 or 8 weeks. The primary endpoint was the change in the HAMD17 score after 6 or 8 weeks of treatment.

Table 2: HAMD17 score for placebo-controlled agomelatine studies with active comparator

Study Treatment	Number of patients	Mean baseline HAMD17 score	Mean HAMD17 score at week 6*	Difference between groups**	95%CI	p
CL3-022						
agomelatine 25mg/d	129	27.6	14.5	1.17°	[-0.59; 2.94]	NS
placebo	147	28.0	15.9			
fluoxetine 20mg/d	133	27.5	13.3	2.55°°	[0.80; 4.31]	0.005
CL3-023						
agomelatine 25mg/d	141	25.7	13.0	0.63°	[-1.21; 2.46	NS
placebo	137	26.0	13.8			
paroxetine 20mg/d	137	26.1	12.2	1.58°°	[-0.27; 3.43]	NS
CL3-024						
agomelatine 25mg/d	148	26.4	12.0	0.90°	[-0.78; 2.58]	NS
agomelatine 50mg/d	147	26.5	13.4	-0.41°	[-2.10; 1.27]	NS
placebo	158	26.9	13.4			
fluoxetine 20mg/d	146	26.5	12.5	0.53°°	[-1.16; 2.22]	NS
CL3-014						
agomelatine 25mg/d	135	27.4	12.8	2.57°	[0.15; 4.99]	0.034
placebo	136	27.4	15.3			
paroxetine 20mg/d	144	27.3	13.1	2.25°°	[0.22; 4.28]	0.030

*LOCF (last observation carry-forward) ** results adjusted to centre and baseline score.
Agomelatine vs. placebo comparator vs. placebo

To conclude, in 3 studies, the efficacy of agomelatine did not differ to that of the placebo. In the fourth study (dose study), the efficacy of 25 mg agomelatine was greater than that of the placebo. The improvement in the HAMD17 depression score observed with agomelatine compared to the placebo was 2.57 points (p=0.034).

[4] Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-ht2c antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol 2002;17:239-47

During these four studies, which included a comparator group to validate the trial's sensitivity, the efficacy of the comparator was greater than that of the placebo in two studies only. In these studies, agomelatine was not compared to the active comparator.

3.1.2. Placebo-controlled efficacy maintenance studies (CL3-021 and CL3-041[5])

The two studies CL3-021 and CL3-041 were aimed at demonstrating the maintained efficacy of agomelatine for 26 and 24 weeks in patients with recurring depressive syndrome.
Patients included had to be aged 18 to 65 and suffer from a major depressive syndrome according to DSM-IV criteria. The HAMD17 scale score had to be at least 22. The patients were treated as outpatients.

There were more inclusion criteria in the second study CL3-041 than in the first. Two other scores were added to the HAMD17 scale: overall level of severity assessed by clinician (CGI-S) and depression intensity (HAD), as well as a questionnaire on the functional impact of the condition on work, social and family life, reported by the patient (SDS).

In both studies, the patients had been previously treated open-label with agomelatine for 8 to 10 weeks. At the end of the open-label phase, patients who had improved (HAMD17 ≤10 and CGI-S = 1 or 2) were randomised into two groups, agomelatine and placebo.

The fixed dose in study CL3-021 and flexible 25-50 mg dose in study CL3-041 were then maintained during the blind period until any relapse for a maximum of 26 and 24 weeks.

The primary endpoint was the accumulated incidence of relapses during a 6-month follow-up period. A relapse was defined as a total HAMD17 score of ≥16, suicide or attempted suicide and for study CL3-041, withdrawal from the trial due to lack of efficacy.

Table 3: Incidence of relapses after 6 months in placebo-controlled agomelatine studies (Kaplan-Meier method)

Study Treatment	Number of randomised patients	Mean baseline HAMD17 score	Accumulated incidence of relapse with agomelatine	Accumulated incidence of relapse with placebo	95%CI	p
CL3-021 agomelatine 25mg/d placebo	187 180	26.3	25.9%	24.8%	[0.674; 1.553]	NS
CL3-041 agomelatine 25-50mg/d placebo	165 174	27.0	21.7%	46.6%	[0.305; 0.690]	0.0001

Analysis based on intention to treat

The accumulated incidence of relapses after 6 months did not differ between placebo and agomelatine in study CL3-021 and was lower in the agomelatine group (21.7%) than in the placebo group (46.6%) (p=0.0001) in study CL3-041.

To conclude, in patients responsive to agomelatine and treated at a flexible dose of 25-50 mg, one of the 2 studies shows a decrease in the accumulated incidence of relapse after 6 months compared to placebo.

[5] Goodwin G, Emsley R, Rembry S, Rouillon F. Agomelatine prevents relapse in patients with major depressive disorder, without evidence of a discontinuation syndrome. J Clin Psy 2009; 70(8):1128-1137

3.1.3. Active comparator-controlled studies

Three active comparator-controlled phase III studies (CL3-045, CL3-035 and CL3-046) were submitted, but only the study comparing to venlafaxine was reviewed by the EMEA to grant the MA due to their tardy completion.

The objective, the comparator and the primary efficacy endpoint differed in each of these studies. Only the study versus fluoxetine compared the antidepressive efficacy using the HAMD17 criteria as the primary endpoint.

The comparators were fluoxetine (SSRI), venlafaxine (SNRI) and sertraline (SSRI).

In the three studies, agomelatine was administered at a flexible dose of 25-50 mg; the comparator doses, although not maximal, correspond to dose levels used in outpatient care.

3.1.3.1. Study CL3-045 versus fluoxetine

This was a randomised, double-blind superiority study comparing the antidepressive efficacy of agomelatine to that of fluoxetine.

Patients included were aged 18 to 65 and suffered from a major depressive episode according to DSM-IV criteria. The HAMD17 scale score had to be at least 25. The patients were treated as outpatients.

Dosages were flexible: agomelatine 25mg-50mg and fluoxetine 20-40 mg Any dosage increases complied with the SPC, after 2 weeks in the agomelatine group and after 4 weeks in the fluoxetine group.

The study lasted 8 weeks followed by an optional double-blind extension for 16 more weeks.

The primary endpoint was short term efficacy according to a HAMD17 scale score at 8 weeks. The delta foreseen when calculating the number of patients was at least 2 points on the HAMD17 scale. The statistical analysis of the primary endpoint was based on the adjusted ANCOVA.

Secondary endpoints included:

- the percentage of responsive patients on the HAMD17 (percentage of patients with decrease in baseline HAMD17 score $\geq$ 50%),
- the quality of sleep according to 4 LSEQ[6] subjective sleep questionnaire items after 8 weeks' treatment),
- the CGI-S scale score,[7]
- the score and percentage of responsive patients on the CGI-I scale[8] (percentage of patients whose CGI-I score was 1 or 2),
- anxiety evaluated on the HAM-A scale[9].

---

[6] LSEQ: Leeds Sleep Evaluation Questionnaire comprising 10 visual analogue scales and looking into the influence of a treatment in terms of improvement or deterioration of 4 subjective sleep items (falling asleep, quality of sleep, waking quality and daytime alertness). Each item can be studied independently. The "falling asleep" item comprises 3 100mm VAS each and the "quality of sleep" item 2 100mm VAS each. Parrott AC, Hindmarch I. Factor analysis of a sleep evaluation questionnaire. Psychol Med 1978;8:325-9

[7] CGI-S: Clinical Global Impressions - Severity scale. The depression severity scale is assessed by the clinician through a score of 0 to 7. Guy W. ECDEU assessment manual for psychopharmacology 028 CGI .1976.

[8] CGI-I: Clinical Global Impression Improvement. The global improvement in depression is assessed by the clinician through a score of 0 to 7. Guy W. ECDEU assessment manual for psychopharmacology 028 CGI .1976

[9] HAM-A Hamilton Rating Scale for Anxiety – Depression severity scale comprising 14 items assessing overall anxiety. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-5

Results
Randomised patients: 515
Mean age: 42; 77.7% women
Mean baseline HAMD17: 28.5 points in the agomelatine group and 28.7 points in the fluoxetine group.
The daily dose was increased, in compliance with the SPC, in 28% of cases after 15 days in the agomelatine group and 20% after 4 weeks in the fluoxetine group.

Results for the primary endpoint:
Table 4: HAMD17 score after 8 weeks (study CL3-045) with agomelatine and fluoxetine

	Number of patients	Mean baseline score	Mean score after 8 weeks (LOCF)	Difference between treatments	95%CI	p
agomelatine	247	28.5	11.1	1.49	0.20 – 2.77	0.024
fluoxetine	257	28.7	12.7			

After 8 weeks' treatment, the difference in HAMD17 score between the agomelatine and fluoxetine groups was 1.49 point (p=0.024) in favour of agomelatine.

30 patients discontinued treatment before 8 weeks (11.9%) in the agomelatine group (7 for inefficacy and 10 for adverse effects) and 45 (17.1%) in the fluoxetine group (13 for inefficacy and 17 for adverse effects).

Secondary endpoint results:
- the percentage of responsive patients according to the HAMD score was 71.7% in the agomelatine group and 63.8% in the fluoxetine group (NS)
- the improvement in sleep disorders according to the LSEQ questionnaire was similar in both groups
- the CGI-S scale[10] score did not differ in the 2 groups
- the CGI-I scale score did not differ between agomelatine and fluoxetine, whereas the percentage of responsive patients (CGI-I score of 1 or 2) was 77.7% in the agomelatine group and 68.8% in the fluoxetine group (p=0.023)
- there was no difference in anxiety between agomelatine and fluoxetine after 8 weeks' treatment

To conclude, this study, of a high methodological standard, demonstrated the statistically superior efficacy of agomelatine over fluoxetine after 8 weeks (1.49 point difference on HAMD17 score).

3.1.3.2. Study CL3-035 versus venlafaxine[11]

This was a randomised, double-blind superiority study comparing the effect of agomelatine to that of venlafaxine on subjective sleep disorders in depressed patients during 6 weeks of treatment.

Patients included had to be aged 18 to 60 and suffer from a major depressive episode according to DSM-IV criteria. The HAMD17 scale score had to be at least 20 (moderate to severe depression). The patients were treated as outpatients.

[10] CGI-S: Clinical Global Impressions - Severity scale. The depression severity is assessed by the clinician using a score of 0 to 7. Guy W. 028 CGI. ECDEU assessment manual for psychopharmacology 1976
[11] Lemoine P, Guilleminault CAE. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double blind comparison with venlafaxine. J Clin Psychiatry 2007;68:1723-32.

The study lasted 6 weeks followed by an optional double-blind extension for 18 more weeks for responsive patients.

Daily dosages were flexible: agomelatine 25-50 mg and venlafaxine 75-150 mg.

The primary endpoint was the “getting to sleep” item of the LSEQ questionnaire measuring the improvement in subjective sleep, evaluated after 1, 2 and 3 weeks’ treatment.

Secondary endpoints included:

- the HAMD17 score after 6 weeks and the percentage of responsive patients (percentage of patients with decrease in baseline HAMD17 score $\geq$ 50%),
- the score and percentage of responsive patients on the CGI-I scale after 6 weeks (percentage of patients whose CGI-I score was 1 or 2),
- other weekly LSEQ items: quality of sleep, quality of awakening and daytime alertness,
- anxiety evaluated using HAM-A score after 6 weeks.

Results

Randomised patients: 332

Mean age: 40; women: 71%

Mean baseline HAMD17: 25.9 points in the agomelatine group and 26.0 points in the venlafaxine group.

The dose was increased in 14% of cases in the agomelatine group and in 10% of cases in the venlafaxine group after 15 days.

15 patients discontinued treatment before 6 weeks (9.0%) in the agomelatine group (3 for inefficacy and 7 for adverse effects) and 36 (21.5%) in the venlafaxine group (3 for inefficacy and 22 for adverse effects).

Results for the primary endpoint:

Table 5: Results for LSEQ questionnaire getting to sleep item (in mm) for agomelatine vs. venlafaxine (study CL3-035)

	Week 1	Week 2	Week 3
Agomelatine25mg-50mg	38.5 +/- 17.0	36.1 +/-17.5	32.4 +/-15.6
Venlafaxine	44.3 +/- 15.9	41.1 +/- 17.2	37.2 +/- 16.4
Difference agomelatine/venlafaxine 95%CI p	5.77 1.79; 9.76 0.005	4.98 0.87; 9.09 0.018	4.78 1.02; 8.55 0.013

After each of the 3 weeks of treatment, the LSEQ subjective sleep questionnaire’s “getting to sleep” item was significantly higher with agomelatine than with venlafaxine. The results are expressed on average over 100 mm.

Secondary endpoint results:

- after 6 weeks’ treatment, no significant difference was observed in the HAMD17 score between agomelatine and venlafaxine (0.92 point difference, p=0.20);

- the number of responsive patients on the HAMD17 scale was not significantly different between the 2 groups;

- after 6 weeks, the difference in CGI-I score was 0.32 points in favour of agomelatine (p=0.016), the percentage of responsive patients was 87.9% with agomelatine and 77.8% with venlafaxine (p=0.015)

- the other LSEQ questionnaire items were significantly different between the groups, in favour of agomelatine:
    - o in the first week of treatment for quality of sleep (p=0.015), maintained after 6 weeks (p=0.041)
    - o at the second week of treatment for waking quality (p=0.008)
    - o only in the first week of treatment for daytime alertness (p<0.0001)

- after 6 weeks' treatment, there was no significant difference between agomelatine and venlafaxine for the HAM-A score (p=0.327).

To conclude, this study demonstrated a greater improvement in the agomelatine group than in the venlafaxine group, for the LSEQ subjective sleep questionnaire's getting to sleep item after 1, 2 and 3 weeks (primary endpoint). The difference between the groups on a 100mm VAS was 5.77mm after 1 week, 4.88mm after 2 weeks and 4.78mm after 3 weeks.

No significant difference was observed in the HAMD17 score as a secondary endpoint between the two groups. It should be noted that this study included less severe depressions (HAMD $\geq$ 20) than in the other studies.

3.1.3.3. Study CL3-046 versus sertraline

This was a randomised, double-blind superiority study comparing the efficacy of agomelatine to that of sertraline, in terms of the relative range of rest/activity cycle profiles in depressive patients.

Patients included were aged 18 to 60 and suffered from a major depressive episode according to DSM-IV criteria. The patients were treated as outpatients. The HAMD17 scale score had to be at least 22 (moderate to severe depression).

The study lasted 6 weeks followed by an optional double-blind extension for 18 more weeks for responsive patients.

Daily dosages were flexible: agomelatine 25-50 mg and sertraline 50-100 mg.
The primary endpoint was the relative range of rest/activity cycle profiles evaluated each week for 6 weeks. Sleep was recorded every day until the end of the 6th week.

Secondary endpoints included:
- the HAMD17 score and the percentage of responsive patients (percentage of patients with decrease in baseline HAMD17 score $\geq$ 50%) after 6 weeks
- the CGI-S score after 6 weeks
- the score and percentage of responsive patients on the CGI-I scale after 6 weeks (percentage of patients whose CGI-I score was 1 or 2)
- the LSEQ questionnaire "getting to sleep" and "quality of sleep" items
- anxiety according to the HAM-A scale after 6 weeks.

Results
Randomised patients: 313
Mean age: 44; 71% women
Mean initial HAMD17: 26.1 points in the agomelatine group and 26.5 points in the sertraline group.

The daily dose was increased in 25% of cases in the agomelatine group and in 24.5% of cases in the sertraline group after 15 days.

21 patients discontinued treatment before 6 weeks (13.6%) in the agomelatine group (4 for inefficacy and 5 for adverse effects) and 30 (18.9%) in the sertraline group (8 for inefficacy and 14 for adverse effects).

Results for the primary endpoint:
At week 1, an improvement in the relative range of rest/activity cycle profiles was observed in the agomelatine group compared to sertraline (p=0.01). This improvement was not observed after week 1.

Secondary endpoint results:

- HAMD17 scale score after 6 weeks of treatment: the difference between the agomelatine group and the sertraline group was 1.68 points (p=0.031) in favour of agomelatine;

- the percentage of responsive agomelatine patients (70.0%) compared to sertraline (61.5%) in terms of HAMD17 score was not significantly different;

- the CGI-S score after 6 weeks was 2.5 in the agomelatine group and 2.8 in the sertraline group (p=0.043);

- the CGI-I score after 6 weeks was 1.8 in the agomelatine group and 2.1 in the sertraline group (p=0.023). There was no significant difference in the percentage of responsive patients in terms of CGI-I score after 6 weeks;

- the results of the LSEQ questionnaire showed no difference after 6 weeks in each of four items. However, during the second week of treatment, the “getting to sleep” (p<0.001) and “quality of sleep” (p=0.025) items were improved more with agomelatine than with sertraline;

- in terms of anxiety, after 6 weeks’ treatment, the HAM-A scale scores were significantly better in the agomelatine group than in the sertraline group (+2.34 points, p=0.017).

To conclude, this study demonstrated an improvement in the relative range of rest/activity cycle profiles with agomelatine compared to sertraline, during the first week of treatment.
The measurement of the antidepressive efficacy based on the HAMD17 score (secondary endpoint) after 6 weeks’ treatment demonstrated a 1.68 point difference in favour of agomelatine compared to sertraline (95%CI [0.15 -3.20] p=0.031)

3.2. Tolerance

In the course of the clinical studies of VALDOXAN, 5,260 patients were given at least one dose of agomelatine, of which over 3,900 depressed patients. The others were healthy volunteers or patients suffering from other conditions. The maximum treatment duration was 19 months. No postmarketing experience from abroad is available.

The SPC indicates mild to moderate adverse effects that generally appeared over the first 2 weeks of treatment. The most common effects were nausea and dizziness. Severe effects were rare (1 case of hepatitis, suicidal thoughts or behaviour of unknown frequency).

The analysis of adverse effects highlights the absence of a significant weight gain compared to the placebo, a small number of gastrointestinal effects and the absence of cardiovascular effects.

The analysis of hepatic effects during the studies showed an increase in transaminases 3 times greater than the upper limit of normal (ULN) in 1.1% of patients, particularly with the 50 mg dose, compared to 0.7% with the placebo. In 7 cases (0.18%) the increase was 10 times the ULN and there was 1 case of cytolytic hepatitis. All increases in transaminases were reversible.

The SPC (section 4.4) recommends "liver function tests should be performed in all patients at initiation of treatment and then periodically after around six weeks (end of acute phase), after around twelve and twenty-four weeks (end of maintenance phase) and thereafter when clinically indicated. Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours. Therapy should be discontinued if the increase in serum transaminases exceeds 3X upper limit of normal and liver function tests should be performed regularly until serum transaminases return to normal."

According to the SPC, the risk of suicide is not yet known. Indeed, this is a rare event and patients with a suicide risk were excluded from the studies. Hence, by analogy with other antidepressants, careful monitoring is foreseen in the risk management plan.

The analysis of sexual adverse effects reported spontaneously and one study on healthy volunteers in comparison to paroxetine demonstrated the safety of agomelatine in terms of sexual function. One randomised, double-blind study on sexual function consequences (CL3-036[12]) involving 277 depressed patients treated with 50 mg agomelatine compared to 150 mg venlafaxine for 12 weeks did not show any significant difference in the total SeXFX score primary endpoint.

The company submitted a study of treatment discontinuation weaning syndrome (CL3-030[13]). This study included 337 patients randomised into 2 groups, double-blind, for 12 weeks. 25 mg agomelatine or 20 mg paroxetine. The remission patients (n=192) were randomised again, either into the active group (continued treatment) or in the placebo group (treatment discontinued), for 2 weeks. The primary endpoint was the average number of weaning symptoms. One week after treatment was discontinued, patients who discontinued agomelatine did not have more weaning symptoms than those who continued agomelatine (difference of -1.41 [95%CI – 3.83; 1.01] (NS), while those who discontinued paroxetine had more weaning symptoms than those who continued paroxetine (difference of 3.83 [95%CI: 1.64; 6.02] ($p<0.001$).

In the phase III studies, very few patients aged over 65 were included. The company has promised the EMEA to conduct a post-authorisation efficacy and acceptability study on agomelatine at the doses of 25 and 50 mg on elderly patients, particularly among those aged over 75.

To conclude, the safety of agomelatine appears to be good in terms of weight, sexual function, cardiovascular and gastrointestinal effects and treatment discontinuation symptoms. However, there has been little follow-up time to ascertain hepatic and suicidal risks, which must be monitored.

---

[12] Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A Double-Blind Comparison of Sexual Functioning, Antidepressant Efficacy, and Tolerability Between Agomelatine and Venlafaxine XR. J Clin Psychopharmacol 2008;28:329-33

[13] Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. Int Clin Psychopharmacol 2004;19:271-80

3.3. Conclusion

The antidepressive efficacy of agomelatine compared to placebo was demonstrated in the short term (6 to 8 weeks) in studies conducted in moderately to severely depressed patients. In 3 of these studies, the improvement in the HAMD17 depression score observed with agomelatine was significantly greater than that of the placebo. The differences in HAMD17 score were 3.44 [95%CI: 1.63; 5.26] p<0.001, 2.30 [95%CI: 0.28; 4.31] p=0.026, 1.17 [95%CI: -0.59; 2.94] NS, 0.63 [IC95%: -1.21; 2.46] NS, 0.90 [95%CI: -0.78; 2.58] NS and -0.41 [95%CI: -2.10; 1.27] NS: 2.57 [95%CI: 0.15 – 4.99] p = 0.034.

The maintenance of the antidepressive effect after 6 months was evaluated in comparison to placebo in two studies on patients responsive to agomelatine. One of these two studies demonstrated an accumulated incidence of relapse after 6 months in patients responsive to agomelatine of 21.7% in the agomelatine group and 46.6% in the placebo group [95%CI: 0.305; 0.690] (p=0.001). The other study did not show any difference between the two groups.

One study versus fluoxetine demonstrated significantly greater efficacy for agomelatine than fluoxetine: 1.49 point difference [95%CI: 0.20; 2.77] p=0.024 in terms of HAMD17 score after 8 weeks. The clinical relevance is difficult to ascertain.

One study versus venlafaxine did not demonstrate any difference in efficacy in terms of HAMD17 score (secondary endpoint) between agomelatine and venlafaxine.

In one study, agomelatine was superior to venlafaxine in terms of the LSEQ questionnaire's "getting to sleep" item in the first 3 weeks. The difference between the groups on a 100mm VAS was 5.7mm after 1 week, 4.98mm after 2 weeks and 4.78mm after 3 weeks, which has little clinical relevance.

One study versus sertraline demonstrated superior efficacy for agomelatine after 6 weeks in terms of the HAMD17 score (secondary endpoint) (p=0.031).

VALDOXAN is tolerated well in terms of weight, sexual function, cardiovascular and gastrointestinal effects and treatment discontinuation symptoms. However, the hepatic effects observed during the studies and the lack of follow-up time to ascertain hepatic and suicide risks require surveillance by healthcare authorities and regular monitoring of transaminases for patients treated.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The main features of a major depressive episode include a depressed mood or a loss of interest in or pleasure from almost every activity. The level of functional impairment linked with a major depressive episode varies, but there is distress and/or impairment at a social or professional level, even if the intensity is only slight. The most serious consequences of a major depressive episode are attempted suicide and actual suicide.

This medicinal product is intended to treat the symptoms of a major depressive episode.

The efficacy/adverse effects ratio for this product is high.

Alternatives are available.

Major depressive episodes are a major public health burden.
Improving their management is a priority public health need (Public Health Act 2004[14]).

In view of the trial data available, in terms of short term efficacy on depression, and the frequency of relapses after 6 months, and in terms of safety on a daily basis (particularly the absence of serotonin syndrome, better safety in terms of weight and sexual function), VALDOXAN is expected to have a low impact on morbidly, mortality and quality of life.
VALDOXAN should therefore provide a partial solution to the identified public health need.
Consequently VALDOXAN is expected to benefit public health in this indication. This benefit is low.

The actual benefit of VALDOXAN in the treatment of major depressive episodes is substantial.

4.2. Improvement in actual benefit

Given the good safety likely to improve compliance to antidepressive treatment and despite its modest efficacy, VALDOXAN provides a minor improvement to actual benefit (IAB IV) in the management of major depressive episodes (characteristic symptoms).

4.3. Therapeutic use [15] [16]

In the case of a minor depressive episode, psychotherapy is proposed as the first-line treatment, depending on how accessible this type of treatment is and the patient's preference. Otherwise, antidepressants may be proposed.

In the case of a moderate depressive episode, antidepressants are proposed as the first-line treatment. A combination of antidepressants and psychotherapy may be proposed in the case of psychosocial problems that have a marked impact on the patient's life.

In the case of a severe depressive episode, antidepressants must be used (grade A). The choice of medicinal product must be limited to medicines for which the SPC mentions the availability of conclusive studies for patients with severe depression. Admission to a psychiatric unit may be necessary, particularly when there is a high risk of suicide, marked somatic consequences, psychotic symptoms or insufficient family and friends.

It is advisable to reassess the response to treatment after 4 to 8 weeks in order to assess its efficacy.

Discontinuing medication for an isolated depressive episode may be discussed 6 months after clinical remission has been achieved. Treatment must be discontinued according to the conditions in the SPC.

[14] Public Health Act 2004- 806 of August 9, 2004: Objective for neuropsychiatric conditions
[15] Outpatient management of an isolated depressive episode in adults – ANAES guidelines, May 2002
[16] Appropriate usage of antidepressants in the treatment of depression and anxiety in adults. Afssaps, October 2006

4.4. Target population

The prevalence of characterised depressive episodes that lasted from one year among the general population can be estimated at around 5%.

On January 1, 2009, the population of metropolitan France and its overseas departments was estimated at 64.3 million inhabitants. The number of adults can be estimated at 50 million. Extrapolating the prevalence data to the French population gives an estimate of 2.5 million adult patients suffering from a major depressive episode.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and/or on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage in the MA.

The Transparency Committee would like to receive the results of a long term study monitoring patients treated with VALDOXAN. The purpose of this study is to document the following parameters under real treatment conditions:

- the characteristics of patients being treated: gender, age, socio-professional category, diagnosis leading to the prescription of VALDOXAN, history of the disease, severity of the depression (HAM scores, effects on quality of life), any relapses, prior treatment (including non-medicinal),
- conditions of use: dosage, frequency and duration of treatment, associated treatments (including psychotherapy), compliance, description of any treatment changes,
- level of VALDOXAN treatment maintenance. Frequency of treatment discontinuations and reasons,
- impact on different anti-depressive efficacy scores and on the quality of life, as well as social and/or professional consequences,
- the middle term safety of this product: how well the benefits are maintained, in terms of serotonin syndrome, weight, sexual disorders and a description of adverse effects (particularly hepatic or suicidal risk).

Patients should be monitored for 1 year.

If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted.

4.5.1. Packaging: appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%