HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

INVEGA 3 mg prolonged-release tablet
Box of 28 tablets (CIP: 381 306-3)

INVEGA 6 mg prolonged-release tablet
Box of 28 tablets (CIP: 381 314-6)

INVEGA 9 mg prolonged-release tablet
Box of 28 tablets (CIP: 381 320-6)

Applicant: JANSSEN-CILAG

paliperidone

List I

ATC Code: N05AX13

Date of marketing authorisation: 25 June 2007 (centralised marketing authorisation)

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Paliperidone

1.2. Indication

Treatment of schizophrenia

1.3. Dosage

Adults
INVEGA is intended for oral administration. The recommended dose of INVEGA is 6 mg once a day in the morning. INVEGA must always be taken at the same time with regard to food. Patients must be told either to always take INVEGA on an empty stomach or to always take it with breakfast, and not to switch between taking it on an empty stomach and taking it with breakfast. No initial dose adjustment is necessary. Some patients may benefit from lower or higher doses within the recommended dose range of 3 to 12 mg once a day. Where dose adjustment is necessary, it must be preceded by a clinical reassessment.

INVEGA must be swallowed whole with liquid and must not be chewed, divided or crushed. The active ingredient is contained within a non-absorbable casing intended to release the active ingredient in a controlled manner. Both the tablet casing and the insoluble ingredients in the core of the tablet are eliminated from the body. Patients do not need to worry if they occasionally notice something looking like a tablet in their stools.

Patients with hepatic insufficiency
No dose adjustment is required in patients with mild or moderate hepatic insufficiency. As INVEGA has not been studied in patients with severe hepatic insufficiency, caution is advised when treating these patients.

Patients with renal insufficiency
The recommended initial dose for patients with mild renal insufficiency (creatinine clearance ≥ 50 and < 80 ml/min) is 3 mg once a day. The dose may be increased according to the patient's clinical response and tolerance.
The recommended initial dose of INVEGA for patients with moderate renal insufficiency (creatinine clearance ≥ 30 and < 50 ml/min) is 3 mg once a day. The recommended initial dose of INVEGA for patients with severe renal insufficiency (creatinine clearance ≥ 10 and < 30 ml/min) is 3 mg every other day. This may be increased to 3 mg once a day after clinical reassessment. As INVEGA has not been studied in patients with creatinine clearance below 10 ml/min, its use is not recommended in these patients.

Elderly patients
The dosage recommendations in elderly patients with normal renal function (≥ 80 ml/min) are the same as those for adults with normal renal function. However, as some elderly patients may have impaired renal function, dose adjustments may be necessary depending on their renal function (see Patients with renal insufficiency above).
INVEGA must be used cautiously in demented elderly patients with risk factors for cerebrovascular accident.

Paediatric use
The safety and efficacy of INVEGA in patients under 18 have not been studied. There is no data on use in children.

Other specific populations
No dose adjustment of INVEGA is recommended on the basis of gender, ethnic origin, or whether a patient smokes.

Transfer to other antipsychotics
There has been no systematic collection of data that would allow the details of transferring patients taking INVEGA to other antipsychotics to be clearly established. As the pharmacodynamic and pharmacokinetic profiles of various antipsychotics vary, patients must be monitored by a doctor where it is thought medically justified to transfer them to a different antipsychotic.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

N	:	Nervous system
N05	:	Psycholeptics
N05A	:	Antipsychotics
N05AX	:	Other antipsychotics
N05AX13	:	Paliperidone

2.2. Medicines in the same therapeutic category

All atypical antipsychotics:

- Amisulpride - SOLIAN and its generic forms
- Clozapine - LEPONEX and its generic forms

(patients who are resistant to treatment, patients who manifest severe neurological side-effects which are impossible to rectify with other antipsychotics, including atypical antipsychotics)

- Loxapine - LOXAPAC
- Olanzapine - ZYPREXA
- Risperidone - RISPERDAL, RISPERDALCONSTA and RISPERDALORO
- Aripiprazole - ABILIFY

2.3. Medicines with a similar therapeutic aim

Other neuroleptics indicated in the treatment of psychoses.

3 ANALYSIS OF AVAILABLE DATA

The pharmaceutical firm submitted five clinical studies that have been assessed by the EMEA for consideration in compiling the dossier:

- 3 studies versus placebo, with an active comparator arm (olanzapine) assessed the efficacy and tolerance of paliperidone in adults suffering from schizophrenia (studies SCH-303, SCH-304, SCH-305).
- 1 study versus placebo assessed the efficacy of paliperidone in preventing relapse in schizophrenic subjects (study SCH-301).
- 1 study versus placebo assessed the efficacy of paliperidone in elderly schizophrenic subjects (study SCH-302).

A 52-week open-label extension phase followed studies SCH 302, 303, 304 and 305. The aim of these open-label studies was to assess long-term tolerance. Efficacy was a secondary criterion. The results of these extension phases will not be described.

The pharmaceutical firm also submitted a study versus olanzapine which has not been assessed by the EMEA (study SCH-3011). Considering the following methodological shortcomings:

- submission of results not in accordance with the initial statistical hypothesis of non-inferiority,
- lack of justification of the choice of the numerical value defining the limit of equivalence,
- per-protocol results not available,

this study was not considered by the Transparency Committee and will therefore not be discussed in detail in this opinion.

3.1 Studies SCH-303, SCH-304 and SCH-305

The three studies had the same objective and methodology, as described in table 1 below.

Table 1: characteristics of studies SCH 303, SCH-304 and SCH-305

	Objective	Methodology	Study populations	Primary efficacy endpoint
Study SCH-303	Assessment of the efficacy and tolerance of paliperidone versus placebo in subjects suffering from schizophrenia.	Randomised double-blind studies versus placebo with an active comparator arm (olanzapine). Duration of studies: 6 weeks	N = 630 Paliperidone 6 mg/d = 123 Paliperidone 9 mg/d = 122 Paliperidone 12 mg/d = 130 Olanzapine 10 mg/d = 128 Placebo = 127 ITT population = 628.	Change in the PANSS[1] score between inclusion and the end of the study on D43 (or the last score value assessed)
Study SCH-304			N = 444 Paliperidone 6 mg/d = 112 Paliperidone 12 mg/d = 112 Olanzapine 10 mg/d = 110 Placebo = 110 ITT population = 432	
Study SCH-305			N = 618 Paliperidone 3 mg/d = 127 Paliperidone 9 mg/d = 125 Paliperidone 15 mg/d = 115 Olanzapine 10 mg/d = 128 Placebo = 123 ITT population = 605	

It should be noted that paliperidone 15 mg is not a dosage listed in the marketing authorisation.

Secondary endpoints:

- Changes in the PSP (*Personal and Social Performance Scale*), CGI-S (*Clinical Global Impression Scale-Severity*) and SQLS (*Symptoms and Quality of life in Schizophrenia Scale*) scores.
- Quality of sleep assessed by a visual analogue scale.
- Proportion of subjects responding to treatments. Subjects are classified as responding to treatment if their PANSS score falls by ≥ 30%.

Inclusion criteria:

- patients aged ≥ 18 years;
- patients who have been suffering from schizophrenia (according to the DSM-IV criteria) for at least one year;
- patients with active symptoms on inclusion and whose PANSS score is between 70 and 120.

Results:

The efficacy results for the primary criterion (change in the PANSS score) relate only to the

[1] PANSS : Positive And Negative Syndrome Scale (score ranging from 30 to 210): sub-scale of positive symptoms (7 items), sub-scale of negative symptoms (7 items), sub-scales of general psychopathology (16 items). The severity of each symptom is ranked from 1 to 7.

paliperidone and placebo groups.
Results for the comparator group (olanzapine) for the same efficacy criterion are available, but it is defined in the study protocol as a secondary criterion. The results for this group are therefore given for information.

Table 2: Results of the SCH-303 study (ITT population)

	Placebo N = 126	**Paliperidone**			*Olanzapine 10 mg N = 128*
		6 mg N= 123	**9 mg N = 122**	**12 mg N = 129**	
Average initial PANSS score	94.1	94.3	93.2	94.6	*93.0*
Change at study end	- 4.1	- 17.9	- 17.2	- 23.3	*- 19.9*
Difference vs placebo p ; 95% CI		- 13.7 < 0.001; [-19.9;-7.5]	- 13.5 < 0.001;[-19.7;-7.3]	- 18.9 < 0.001;[-25;-12.8]	
Difference vs olanzapine 95% CI		- 2.4 [-7.4;2.5]	- 2.7 [-7.6; 2.3]	2.9 [-2.0; 7.8]	
Proportion of subjects responding	30 %	56 %	51 %	61 %	*51.6 %*

Table 3: Results of the SCH-304 study (ITT population)

	Placebo N = 105	**Paliperidone**		*Olanzapine 10 mg N = 105*
		6 mg N= 111	**12 mg N = 111**	
Average initial PANSS score	93.6	92.3	94.1	*94.9*
Change at study end	- 8.0	- 15.7	- 17.5	*- 18.4*
Difference vs placebo p ; 95% CI		- 7.0 0.006; [-12.3;-1.8]	- 8.5 < 0.001;[-13.8;-3.3]	
Difference vs olanzapine 95% CI		- 1.6 [-6.4;3.2]	- 0.3 [-5.0;4.5]	
Proportion of subjects responding	34.3 %	50 %	51.4 %	*45.7 %*

Table 4: Results of study SCH-305 (ITT population)

	Placebo N = 120	**Palipéridone**			*Olanzapine 10 mg N = 126*
		3 mg N= 123	**9 mg N = 123**	**15 mg N = 113**	
Average initial PANSS score	93.9	91.6	93.9	92.4	*93.3*
Change at study end	- 2.8	- 15.0	- 16.3	- 19.9	*- 18.1*
Difference vs placebo p ; 95% CI		- 11.6 < 0.001; [-17.2;-6.1]	- 12.9 < 0.001;[-18.4;-7.4]	- 17.2 <0.001;[-22.8;-11.5]	
Difference vs olanzapine 95% CI		- 2.6 [-7.0;1.8]	- 1.2 [-5.6;3.2]	3.1 [-1.5;7.6]	
Proportion of subjects responding	18.3 %	39.8 %	45.5 %	52.7 %	*52.4 %*

Tolerance:
In these three studies, 72% of patients treated with paliperidone experienced adverse events (AE). The corresponding figures for patients treated with placebo and olanzapine were 66% and 69% respectively. The AE most frequently observed were central nervous system disorders, psychiatric disorders, gastrointestinal disorders and cardiac disorders.
The AE that may have been linked to treatment and that were observed in more than 2% of patients treated with paliperidone were as follows: headache (13.2%) tachycardia (6.6%), akathisia (6.5%), sinus tachycardia (5.5%), extrapyramidal disorders (5.4%), drowsiness (4.9%), vertigo (4.8%), sedation (4.2%), tremor (3.4%), hypertension (2.8%), dystonia (2.6%), orthostatic hypotension (2.5%) and dry mouth (2.4%).
Drowsiness was less frequent in patients treated with paliperidone than in patients treated with olanzapine: 5% versus 13% (3% in the placebo group).
The rates of clinically significant weight gain (≥ 7%) were 18% in the olanzapine and paliperidone 15 mg groups, 6% to 9% in the other paliperidone groups and 5% in the placebo groups.

Serious AE rates were around 6% in all three treatment group, and consisted mainly of psychotic or schizophrenic disorders.

Conclusion:
Analysis of these three studies showed that in patients suffering from schizophrenia a significantly greater reduction in the PANSS score after six weeks of treatment was observed in patients treated with paliperidone compared with patients treated with placebo, irrespective of the daily dose of paliperidone (3 mg, 6 mg, 9 mg, 12 mg or 15 mg). Depending on the studies, this difference between the paliperidone groups and placebo groups ranged from -7 to -18.9, with initial PANSS scores of between 91.6 and 94.6.
The quantitative effect of paliperidone in these three studies is similar to that observed with olanzapine 10 mg (recommended initial dose).
Among the secondary endpoints, the proportion of patients responding to treatment was higher in the paliperidone groups than in the placebo groups, ranging from 39.8% to 61% in the paliperidone groups compared with 18.3% to 34.3% in the placebo groups.

In terms of tolerance, adverse events were frequent in all treatment groups: 72% in the paliperidone group, 66% in the placebo group and 69% in the olanzapine group.
The Transparency Committee emphasises the fact that adverse events were frequent in patients treated with placebo, at a rate comparable to that among patients treated with one of the two antipsychotics.

3.2 Study SCH-301

It is a randomised double-blind study versus placebo with the primary objective of assessing the efficacy of paliperidone in preventing relapse in patients suffering from schizophrenia. This study has been followed by an open-label extension phase.
Prior to the study, patients were treated with paliperidone on an open-label basis until the optimum dose allowing them to achieve equilibrium was found. Following this titration, the patients were assigned at random to treatment with the active drug or with placebo on a double-blind basis.
Inclusion criteria: the same as for studies SCH-303, 304 and 305.
Principal efficacy endpoint: length of time to relapse.
Results: the study included 530 patients, average age 37.9, of whom 207 were assigned at random to treatment with the active drug or with placebo (paliperidone group n = 105; placebo group n = 102). The average dose of paliperidone in the double-blind period was 10.8 mg/day.
The relapse rate among patients treated with paliperidone was significantly lower than that among patients treated with placebo: 22.1% (23/104) versus 51.5% (52/101) ($p < 0.001$). The estimated time for 25% of patients undergoing treatment to relapse was 68 days in the paliperidone group versus 23 days in the placebo group.

The patients included in the double-blind phase versus placebo had previously undergone open-label treatment with paliperidone. Patients who did not achieve equilibrium during this open-label phase were excluded from the study; this means that all the patients included in the double-blind phase responded to paliperidone.
The Transparency Committee regrets the lack of an active comparator arm.

3.3 Study SCH-302

It is a randomised double-blind study versus placebo with the primary objective of assessing the efficacy and tolerance of paliperidone (3 mg to 12 mg) in patients aged 65 or over suffering from schizophrenia.
The duration of the study was 6 weeks.
Inclusion criteria: patients aged over 65 suffering from schizophrenia (according to the DSM-IV criteria) for at least one year, with a PANSS score between 70 and 120.
Primary efficacy endpoint: change in the PANSS score.
Results:

Table 5: Results of the SCH-302 study (ITT population)

	Placebo N = 38	**Paliperidone N=76**
Average age (SD)	69.1 (3.34)	70,1 (4,95)
Average initial PANSS score	94.3	91,8
Change at study end	-9.9	-14,6
Difference vs placebo **p ; 95% CI**	-5.5 <0.05 ; [-9.85;-1.12]	

The average dose of paliperidone was 8 mg a day.
The fall in the PANSS score was significantly greater in the paliperidone group than in the placebo group: -14.6 versus -9.9 (Δ = -5.5, 95% CI [-9.85;-1.12]).
Thirty eight percent of patients in the paliperidone group responded to treatment, compared with 29% in the placebo group. The difference between these two groups is not significant.
Adverse events (AE) were observed in 67% of patients in the paliperidone group versus 71% in the placebo group.
According to the EPAR, the following AE were more frequent in the paliperidone group than in the placebo group: drowsiness (9% vs 5%), vertigo (7% vs 0%), hypotension (5% vs 0%), tachycardia (16% vs 0%), and QT segment prolongation (7% vs 3%).

Conclusion:
This study showed paliperidone (3 mg to 12 mg) to be effective in subjects aged over 65 and suffering from schizophrenia: the difference in the fall in the PANSS score after six weeks of treatment was -5.5 between the paliperidone group and the placebo group (p<0.005, 95% CI [-9.85;-1.12]).
It should be noted that there was a non negligible response to treatment in the placebo group:

- 29% of subjects in this group responded to treatment, as against 38% in the paliperidone group (NS);
- the fall in the PANSS score was -9.9 in the placebo group versus -14.6 in the paliperidone group: 10.5% in the placebo group versus 15.9% in the paliperidone group;

In terms of tolerance, the type and frequency of adverse events were similar to those observed in the studies SCH-303, 304 and 305.

3.4 Conclusion

The studies SCH-303, 304 and 305 showed the efficacy of paliperidone in changing the PANSS score, versus treatment with placebo, in patients suffering from schizophrenia, irrespective of their daily dose of paliperidone (3 mg, 6 mg, 9 mg, 12 mg or 15 mg).
Study SCH-301 showed that paliperidone remained effective in patients who initially responded to this treatment: the estimated time for 25% of patients undergoing treatment to suffer a relapse was 68 days in the paliperidone group versus 23 days in the placebo group.
The efficacy of paliperidone versus placebo in subjects aged over 65 and suffering from schizophrenia was demonstrated in study SCH-302.
The Transparency Committee regrets the lack of long-term efficacy data and the lack of a study versus an active comparator, in particular versus risperidone.

The adverse events most frequently observed were central nervous system disorders, psychiatric disorders, gastrointestinal disorders and cardiac disorders.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The main features of schizophrenia are the presence of a set of signs and symptoms described as positive (delusions, hallucinations, disordered speech, severely disordered or catatonic behaviour) or negative (affective dulling, alogia, loss of will) associated with a clear social or activity-related malfunction.
Schizophrenia evolves in various ways: some patients experience exacerbations and remissions, while others remain chronically affected. Some patients seem to evolve in a relatively stable manner, while others manifest progressive aggravation and severe incapacity.

This proprietary drug provides symptomatic treatment.

It is used for first-line therapy.

The efficacy/safety ratio for this proprietary drug is high.

Alternative proprietary drugs exist.

Schizophrenia presents a major public health burden in view of the frequency and severity of the condition.

The need for improved management of schizophrenia is still a public health need in the context of a priority established by the GTNDO* (National Technical Group for Defining Public Health Objectives).

In the light of the data available (in particular: mainly studies versus placebo; insufficient data versus existing treatment; lack of data on relapses and frequency of hospitalisation), INVEGA is not expected to have any additional impact on morbidity and quality of life for schizophrenic patients compared to available treatments.

Furthermore, it is not certain that the results of trials can be transposed into clinical practice in view of the doubts as to long-term observance.

The proprietary drug INVEGA is therefore unlikely to be able to meet the identified public health need.

Consequently, in the current state of knowledge, the proprietary drug INVEGA is not expected to have any public health benefit.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

While awaiting the reassessment of the entire class of antipsychotics, the opinion is:

INVEGA, the main active metabolite of risperidone, does not provide any improvement in actual benefit (IAB V) in the therapeutic management of schizophrenia.

4.3. Therapeutic use

Neuroleptics have been proven to be effective in the treatment of cases of schizophrenia, especially with regard to the positive symptoms.

Two-thirds to three-quarters of patients will suffer adverse events caused by these treatments during their lifetime (mental effects, neurological effects (especially extrapyramidal effects), vegetative effects, endocrinal effects).

According to the most recent recommendations of the WFSBP[2] (World Federation of Societies of Biological Psychiatry), atypical antipsychotics (also referred to as "second generation" antipsychotics) are used as first-line treatment in cases of early-stage schizophrenia. Conventional antipsychotics (or "first generation" psychotics) can be used as an alternative. They should be administered at the lowest effective dose to minimise extrapyramidal adverse events, and tolerance should be monitored particularly carefully in these patients.

Atypical antipsychotics seem to be preferred during recurrent episodes, although conventional antipsychotics also have their place in the treatment of acute phases. Antipsychotics should be selected in accordance with various factors, in particular patient preferences arising from past experience of treatment (response to treatment and tolerance), the administration route, comorbidities and potential interactions with other treatments.

Long-term treatment must be established in order to stabilise the patient's condition; this will help improve the efficacy of psychological treatments and prevent relapses. Atypical or conventional antipsychotics are indicated in this situation. Conventional antipsychotics can continue to be prescribed for patients who have not suffered any major adverse events.

These recommendations are in line with those of NICE[3] (National Institute for Clinical Excellence, 2002) and those issued following the consensus conference of the French Federation of Psychiatry[4] (2003). However, the question of whether atypical antipsychotics are superior to conventional antipsychotics in terms of efficacy and tolerance has yet to be

[2] Falkai P. et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. World J Biol Psychiatry 2005; 6 (4): 132 – 191 Part 2 : long term treatment of schizophrenia World J Biol Psychiatry 2006,7(1) : 132-191

[3] Schizophrenia- Core interventions in the treatment and management of schizophrenia in primary and second care- NICE 2002

[4] Schizophrénies débutantes : diagnostic et modalités thérapeutiques - Conférence de consensus [Early-stage schizophrenia: diagnosis and details of treatment - consensus conference] ANAES, 23-24 January 2003

resolved. Whichever antipsychotic is used, the dosage must be adjusted to limit the occurrence of neurological, cardiovascular, metabolic and endocrinal adverse events.

Treatment using a single antipsychotic is preferred, administered orally if possible.
In some cases, particularly at the start of an acute psychotic episode, the presence of anxiety and/or agitation alongside delusions can lead practitioners to add a sedative polarity drug (benzodiazepine or anxio-sedative antipsychotic) to an anti-delusional antipsychotic.

Patients suffering from schizophrenia require a multi-dimensional approach. Drug treatments should be combined with individual or group psychotherapy, institutional or family management, and social interventions.

4.4. Target population

The annual incidence of schizophrenic disorders is in the order of 0.1 per 1,000 inhabitants.
Its prevalence is roughly 1% among the general population.
In France, it is estimated that 400,000 people suffer from schizophrenia, with 10,000 new cases a year[5].

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services in the extension of the indication and at the dosage of the marketing authorisation.

4.5.1 Packaging

Appropriate for the prescription conditions in the indication.

4.5.2 Reimbursement rate: 65%

[5] Hautecouverture S et al. Epidémiologie des troubles schizophréniques [Epidemiology of schizophrenic disorders]. Presse Med 2006 ; 35 (volume 2) : 461-8.