The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

1 February 2012

XEPLION 25 mg, prolonged-release suspension for injection
1 pre-filled polycycloolefin syringe with 2 needles (CIP code: 417 665-8)

XEPLION 50 mg, prolonged-release suspension for injection
1 pre-filled polycycloolefin syringe with 2 needles (CIP code: 417 666-4)

XEPLION 75 mg, prolonged-release suspension for injection
1 pre-filled polycycloolefin syringe with 2 needles (CIP code: 417 667-0)

XEPLION 100 mg, prolonged-release suspension for injection
1 pre-filled polycycloolefin syringe with 2 needles (CIP code: 417 668-7)

XEPLION 150 mg, prolonged-release suspension for injection
1 pre-filled polycycloolefin syringe with 2 needles (CIP code: 417 669-3)

XEPLION 150 mg and XEPLION 100 mg, prolonged-release suspension for injection
1 150-mg pre-filled polycycloolefin syringe with 2 needles - 1 100-mg pre-filled polycycloolefin syringe with 2 needles (CIP code: 417 670-1)

Applicant: JANSSEN-CILAG

Paliperidone (palmitate)
ATC code: N05AX13 (antipsychotic)

List I

Date of Marketing Authorisation (centralised procedure): 04/03/2011

Reason for request: Inclusion on the list of medicines refundable by National Insurance and approved for hospital use

Medical, Economic and Public Health Assessment Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Paliperidone palmitate (active metabolite of risperidone)

1.2. Indications
“XEPLION is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.
In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long acting injectable treatment is needed.”

1.3. Dosage and method of administration (see SPC)
Dosage
“Recommended initiation of XEPLION is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle then a monthly maintenance dose of 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Previous oral paliperidone or oral risperidone can be discontinued at the time of the initiation of treatment with XEPLION. XEPLION should be initiated as described at the beginning of section 1.3 above.

When switching patients from risperidone long acting injection, initiate XEPLION therapy in place of the next scheduled injection. XEPLION should then be continued at monthly intervals. The one-week initiation dosing regimen including the intramuscular injections (day 1 and 8, respectively) as described section 1.3 above is not required. Patients previously stabilised on different doses of risperidone long acting injection can attain similar paliperidone steady-state exposure during maintenance treatment with XEPLION monthly doses as set out in the SPC.”

Method of administration
“XEPLION is intended for intramuscular use only. It should be injected slowly, deep into the muscle. The day 1 and 8 initiation doses must each be administered in the deltoid muscle in order to attain therapeutic concentrations rapidly. Following the second dose, monthly maintenance doses can be administered in either the deltoid muscle or gluteal muscle. A switch from gluteal to deltoid (and vice versa) should be considered in the event of injection site pain if the injection site discomfort is not well tolerated. It is also recommended to alternate between left and right sides.”
2.1. ATC Classification (2010)

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

2.2. Medicaments in the same therapeutic category

- Long acting injectable antipsychotics

<table>
<thead>
<tr>
<th>INN (medicinal products)</th>
<th>MA date</th>
<th>MA indications</th>
<th>AB</th>
<th>IAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupentixol (FLUANXOL LP)</td>
<td>1983</td>
<td>Long-term treatment of chronic psychotic states (schizophrenia, chronic non-schizophrenic delirium: paranoid delirium, chronic hallucinatory psychoses)</td>
<td>substantial</td>
<td>NA</td>
</tr>
<tr>
<td>Fluphenazine (MODECATE)</td>
<td>1992</td>
<td>Long-term treatment of chronic psychotic states (schizophrenia, chronic non-schizophrenic delirium: paranoid delirium, chronic hallucinatory psychoses)</td>
<td>substantial</td>
<td>NA</td>
</tr>
<tr>
<td>Haloperidol (HALDOL DECANOAS)</td>
<td>1983</td>
<td>Long-term treatment of chronic psychotic states (schizophrenia, chronic non-schizophrenic delirium: paranoid delirium, chronic hallucinatory psychoses)</td>
<td>substantial</td>
<td>NA</td>
</tr>
<tr>
<td>Olanzapine (ZYPADHERA)</td>
<td>2008</td>
<td>Maintenance treatment in adult schizophrenic patients sufficiently stabilised with oral olanzapine during the initial phase of the treatment</td>
<td>moderate</td>
<td>V</td>
</tr>
<tr>
<td>Pipotiazine (PIPORTIL)</td>
<td>1988</td>
<td>Long-term treatment of chronic psychotic states (schizophrenia, chronic non-schizophrenic delirium: paranoid delirium, chronic hallucinatory psychoses)</td>
<td>substantial</td>
<td>NA</td>
</tr>
<tr>
<td>Risperidone (RISPERDALCON STA LP)</td>
<td>2003</td>
<td>Maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics</td>
<td>substantial</td>
<td>IV*</td>
</tr>
<tr>
<td>Zuclopenthixol (CLOPIXOL)</td>
<td>1987</td>
<td>Chronic psychotic states (schizophrenia, chronic non-schizophrenic delirium: paranoid delirium, chronic hallucinatory psychoses) Serious behavioural disorders in children with agitation and aggressiveness</td>
<td>substantial</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: not assigned; *"As no clinical data are available making it possible to place this medicinal product precisely in relation to the other antipsychotics recommended in the treatment of patients suffering from schizophrenic psychosis, the Commission maintains the IAB IV assigned on 2 June 2004 to RISPERDALCONSTA LP as the method of administration likely to improve management of these patients." (TC opinion of 05/05/2010)

- Oral antipsychotics indicated in the treatment of schizophrenia

**Oral paliperidone is not available in France.**
3 ANALYSIS OF AVAILABLE DATA

3.1. Short-term efficacy data

XEPLION has been the subject of four short-term, phase-III clinical studies:

- Three 13-week studies (PSY-3003, PSY-3004, PSY-3007) aimed at demonstrating XEPLION's superiority versus placebo in adult patients with schizophrenia in the acute phase;
- One 13-week study (PSY-3006) aimed at demonstrating XEPLION's non-inferiority versus RISPERDALCONSTA LP in adult patients with schizophrenia.

3.1.1. Studies versus placebo (PSY-3003, PSY-3004 and PSY-3007)

a) Methodology

The three studies (PSY-3003, PSY-3004, and PSY-3007) compared the efficacy and tolerability of XEPLION over 13 weeks at fixed doses (25, 50, 100, 150 mg) with placebo in adult patients in the acute phase of schizophrenia.

The fixed doses of XEPLION were administered on days 1, 8, 36 and 64 (see table 1).

The subjects were hospitalised for a minimum period of 8 days after the first injection.

Table 1. Description of the three studies versus placebo PSY-3003, PSY-3004, and PSY-3007

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>XEPLION doses</th>
<th>Injection site</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSY-3003</td>
<td>DB, placebo, 3 fixed doses</td>
<td>50, 100 or 150 mg on D1, D8, D36 and D64</td>
<td>Gluteal muscle</td>
<td>13</td>
</tr>
<tr>
<td>PSY-3004</td>
<td>DB, placebo, 3 fixed doses</td>
<td>25, 50 or 100 mg on D1, D8, D36 and D64</td>
<td>Gluteal muscle</td>
<td>13</td>
</tr>
<tr>
<td>PSY-3007</td>
<td>DB, placebo, 3 fixed doses</td>
<td>150 mg on D1 followed by 25, 100 or 150 mg on D8, D36 and D64</td>
<td>1st injection in the deltoid muscle, followed by injections in the deltoid or gluteal muscles</td>
<td>13</td>
</tr>
</tbody>
</table>

DB : double-blind

The subjects included were adults with schizophrenia (DSM-IV) for at least one year with a total PANSS\(^1\) score on inclusion between a minimum of 60 or 70 and a maximum of 120.

The main criterion was progression of the total score on the PANSS scale after 13 weeks of treatment compared with the value on inclusion.

The main secondary criteria included:
- Progression of overall severity of the disease measured by the CGI-S scale\(^2\);
- Progression of the patient's personal and social performance evaluated by the PSP scale\(^3\);
- The percentage of responders (response being defined as an improvement on the PANSS total score of 30% or more).

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\(^1\) The PANSS scale (Positive and Negative Syndrome Scale) includes 30 items, graded from 1 (symptom absent) to 7 (symptom extremely severe), divided into 3 groups: 7 items form part of a positive scale, another 7 form a negative scale. The remaining 16 constitute a general psychopathology scale.

\(^2\) The CGI-S scale (Clinical Global Impression–Severity) is graded from 1 (not ill) to 7 (extremely severe). This scale provides an overall evaluation of the patient at a given time.

\(^3\) The PSP (Personal and Social Performance) scale is a scale of performance and personal and social development.
b) Results

The results on the progression of the PANSS score are detailed in table 2.

Table 2. Rate of early discontinuation and progression of the PANSS score in the PSY-3003, PSY-3004 and PSY-3007 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arm</th>
<th>n</th>
<th>% early discontinuation</th>
<th>PANSS mean inclusion (SD)</th>
<th>Mean change (SD)</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSY-3003</td>
<td>Placebo</td>
<td>136</td>
<td>63</td>
<td>92.4 (12.55)</td>
<td>-4.1 (21.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pal. 50 mg</td>
<td>94</td>
<td>50</td>
<td>89.9 (10.78)</td>
<td>-7.9 (18.71)</td>
<td>0.193</td>
</tr>
<tr>
<td></td>
<td>Pal. 100 mg</td>
<td>97</td>
<td>45</td>
<td>90.1 (11.66)</td>
<td>-11.0 (19.06)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Pal. 150 mg</td>
<td>30</td>
<td>60</td>
<td>92.2 (11.72)</td>
<td>-5.5 (19.78)</td>
<td></td>
</tr>
<tr>
<td>PSY-3004</td>
<td>Placebo</td>
<td>127</td>
<td>62</td>
<td>90.7 (12.22)</td>
<td>-7.0 (20.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pal. 25 mg</td>
<td>131</td>
<td>47</td>
<td>90.7 (12.25)</td>
<td>-13.6 (21.45)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Pal. 50 mg</td>
<td>129</td>
<td>46</td>
<td>91.2 (12.02)</td>
<td>-13.2 (20.14)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>Pal. 100 mg</td>
<td>131</td>
<td>43</td>
<td>90.8 (11.70)</td>
<td>-16.1 (20.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSY-3007</td>
<td>Placebo</td>
<td>164</td>
<td>57</td>
<td>86.8 (10.31)</td>
<td>-2.9 (19.26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pal. 25 mg</td>
<td>160</td>
<td>48</td>
<td>86.9 (11.99)</td>
<td>-8.0 (19.90)</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Pal. 100 mg</td>
<td>165</td>
<td>46</td>
<td>86.2 (10.77)</td>
<td>-11.6 (17.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Pal. 150 mg</td>
<td>163</td>
<td>45</td>
<td>88.4 (11.70)</td>
<td>-13.2 (18.48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD : standard deviation; Pal. : paliperidine palmitate

▪ **Study PSY-3003**

In all, 388 patients were randomised. There were 45% to 60% of early discontinuations in the XEPLION arm and 63% in the placebo arm. The main reason for discontinuation was the lack of efficacy whatever the treatment arm.

XEPLION was superior to placebo in reducing the PANSS score at the dose of 100 mg but not at the dose of 50 mg. In the XEPLION 150 mg arm, the rate of early discontinuation was 60% and the reduction in the PANSS score was – 5.5 (standard deviation [SD] : 19.8)⁵.

▪ **Study PSY-3004**

In all, 518 patients were randomised. There were 43% to 47% of early discontinuations in the XEPLION arm and 62% in the placebo arm. The main reason for discontinuation was the lack of efficacy whatever the treatment arm.

All the doses of XEPLION tested (25 mg, 50 mg or 100 mg) were superior to placebo in reducing the PANSS score and the CGI-S score.

No difference was observed between the XEPLION and placebo arms in the progression of the PSP score. The results on the responder rate were favourable to XEPLION except at the dose of 50 mg (p = 0.271).

▪ **Study PSY-3007**

In all, 652 patients were randomised. There were 45% to 48% early discontinuations in the XEPLION arm and 62% in the placebo arm. The main reasons for discontinuation were : lack of efficacy in the placebo arm, lack of efficacy and withdrawal of consent in the XEPLION arms.

XEPLION was superior to placebo in reducing the PANSS score whatever the dose (25 mg, 100 mg or 150 mg). A dose-response effect was observed with a bigger reduction in the PANSS score for the higher doses of XEPLION. XEPLION’s superiority to placebo was also observed in the secondary criteria (CGI-S and PSP scores and responder rate) at the 100 and 150 mg doses but not at the 25 mg dose.

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⁴ Because of an error in allocating the treatment kits, more patients were included in the placebo group than envisaged and only 30 patients were included in the XEPLION 150 mg arm instead of 90.

⁵ The statistical analysis laid down in the protocol specified that the difference between XEPLION 150 mg and placebo would be tested only in the event of superiority of the XEPLION 50 mg and 100 mg arms over placebo.
3.1.2. Study versus RISPERDAL CONSTA LP (PSY-3006)

a) Methodology

Study PSY-3006 is a randomised, double-blind, comparative study versus RISPERDAL CONSTA LP.

The main objective was to demonstrate non-inferiority of XEPLION compared with RISPERDAL CONSTA LP in the treatment of schizophrenia symptoms.

The subjects included were adults with schizophrenia (DSM-IV) for at least one year with a total PANSS score on inclusion of between 60 and 120.

The patients were randomised into two parallel groups (1:1) to receive XEPLION or RISPERDAL CONSTA LP.

The doses and injection sites are set out below:

<table>
<thead>
<tr>
<th>Day</th>
<th>Injection</th>
<th>XEPLION</th>
<th>Injection site</th>
<th>RISPERDAL CONSTA LP</th>
<th>Injection site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150 mg Placebo</td>
<td>Deltoid</td>
<td>Placebo 1-6 mg/d</td>
<td>Deltoid</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>100 mg Placebo</td>
<td>Deltoid</td>
<td>25 mg 1-6 mg/d</td>
<td>Deltoid</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Placebo Placebo</td>
<td>Gluteal</td>
<td>25 mg 1-6 mg/d</td>
<td>Gluteal</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>50 or 100 mg Optional placebo</td>
<td>Deltoid or Gluteal</td>
<td>25-37.5 mg Optional risperidone</td>
<td>Deltoid or Gluteal</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Placebo Optional placebo</td>
<td>Gluteal</td>
<td>25-37.5 mg Optional risperidone</td>
<td>Gluteal</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>50, 100 or 150 mg Optional placebo</td>
<td>Deltoid or Gluteal</td>
<td>25-50 mg Optional risperidone</td>
<td>Deltoid or Gluteal</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>Placebo Optional placebo</td>
<td>Gluteal</td>
<td>25-50 mg Optional risperidone</td>
<td>Gluteal</td>
<td></td>
</tr>
</tbody>
</table>

The main criterion was a change in the total score on the PANSS scale since inclusion. To demonstrate non-inferiority, the lower limit of the unilateral confidence interval at 97.5% had to be higher than -5 points.

The main secondary criteria were:
- Progression of overall severity of the disease measured by the CGI-S scale;
- Progression of the patient’s personal and social performance evaluated by the PSP scale.

b) Results

In all, 1,220 patients were randomised. In the per-protocol population (765 patients), 328 (84%) patients of the XEPLION arm and 319 patients (85%) of the RISPERDAL CONSTA LP arm completed the study.

At 13 weeks, the mean change in the PANSS score was -18.6 (SD : 15.4) in the XEPLION arm and – 17.9 (SD : 14.2) in the RISPERDAL CONSTA LP arm. XEPLION was not inferior to RISPERDAL CONSTA LP with a mean difference change in the PANSS score of 0.4 (95% CI [-1.62; 2.38]) between the two arms (see table 3).
Table 3. Change in the total score of the PANSS scale compared with inclusion in study PSY-3006 (per-protocol population-LOCF6)

<table>
<thead>
<tr>
<th></th>
<th>XEPLION</th>
<th>RISPERDALCONSTA LP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 389)</td>
<td>(n = 376)</td>
</tr>
<tr>
<td><strong>Start of the study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>84.9 (11.53)</td>
<td>83.5 (10.92)</td>
</tr>
<tr>
<td>Median (extremes)</td>
<td>84.0 (62; 120)</td>
<td>83.0 (60; 115)</td>
</tr>
<tr>
<td><strong>End of the study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.2 (16.40)</td>
<td>65.6 (15.58)</td>
</tr>
<tr>
<td>Median (extremes)</td>
<td>65.0 (31; 152)</td>
<td>66.0 (32; 129)</td>
</tr>
<tr>
<td><strong>Change since inclusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-18.6 (15.45)</td>
<td>-17.9 (14.24)</td>
</tr>
<tr>
<td>Median (extremes)</td>
<td>-18.0 (-74; 75)</td>
<td>-17.0 (-58; 50)</td>
</tr>
<tr>
<td>Difference in the Upper Limit means</td>
<td>0.4 (1.02)</td>
<td>(-1.62; 2.38)</td>
</tr>
</tbody>
</table>

No difference was observed between the two arms in improvement of the mean severity scores on the CGI-S scale (intention-to-treat population).
The results of the intention-to-treat analysis were consistent with those of the per-protocol analysis.

3.2. Long-term efficacy data

XEPLION has been the subject of two long-term, phase-III studies:
- One 52-week study (PSY-3001) aimed at demonstrating XEPLION’s superiority over placebo in preventing schizophrenic relapses;
- One 53-week study (PSY-3002) aimed at demonstrating XEPLION’s non-inferiority compared with RISPERDALCONSTA LP in adult patients with schizophrenia.

3.2.1. Study versus placebo (PSY-3001)

a) Methodology

Study PSY-3001 is a randomised, double-blind, comparative study versus placebo in adult patients with schizophrenia.

The main objective was to demonstrate XEPLION’s superiority over placebo in preventing relapses of schizophrenia symptoms.

The subjects included were adults with schizophrenia (DSM-IV) for at least one year with a total PANSS score on inclusion of less than 120.

This study included (see figure 1):
- A 9-week, open transition phase during which the treatment with XEPLION was set up: XEPLION was administered at a dose of 50 mg on day 1 and day 8, then 25, 50 or 100 mg in week 5.
- A 24-week, open maintenance phase for stabilised patients (a PANSS score of ≤ 75 in week 9): XEPLION was administered at a flexible dose for the 12 first weeks (25, 50 or 100 mg), then at a fixed dose in the following 12 weeks on the basis of the last dose received.
- A comparative, double-blind relapse-prevention phase versus placebo in eligible patients (a PANSS score ≤ 75 at the end of the maintenance phase and a PANSS score ≤ 4 on 7 items of the PANSS) during which the patients included were randomised (1 : 1) to receive placebo or XEPLION at the dose defined during the maintenance phase.
- An optional 52-week open phase during which relapsers received XEPLION.
An intermediate analysis of efficacy was planned after the onset of 68 relapses.

The main criterion was the time to onset of a first relapse during the double-blind phase. This time was defined as the time that has elapsed between randomisation carried out at the start of the double-blind phase and the first documentation of relapse\(^7\). The main secondary criteria were the progression in the scores on the PANSS, CGI-S and PSP scales.

**Figure 1. PSY-3001 study design**

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\(^7\) The relapse criteria were defined as follows:

a) Hospitalisation for a psychiatric reason (voluntary admission or under constraint in the psychiatric hospital for decompensation of the psychotic symptoms), or

b) A 25% increase in the PANSS score between randomisation and 2 consecutive measurements separated by 3 to 7 days if the PANSS score at the time of randomisation was > 40, or

c) A 10-point increase in the total PANSS score between randomisation and 2 consecutive measurements separated by 3 to 7 days if the score at the time of randomisation was ≤ 40, or

d) Deliberate self-mutilation and/or violent behaviour resulting in suicide or in clinically significant harm to self or others or damage to property, or

e) Onset of suicidal ideas or homicide and aggressive behaviour judged to be clinically significant (in frequency and seriousness) by the investigator, or

f) For the following items on the PANSS scale: item P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinatory behaviour), P6 (suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness): a score ≥ 5 after randomisation in 2 consecutive evaluations separated by 3 to 7 days on one of the above items if the maximum PANSS score for the above items was ≤ 3 at the time of randomisation, or a score ≥ 5 after randomisation in 2 consecutive evaluations separated by 3 to 7 days on one of the above items if the maximum PANSS score for the above items was ≥ 4 at the time of randomisation.
b) Results

The study was discontinued early at the end of the intermediate analysis (after 68 relapses) because of the results favourable to XEPLION.

In all, 849 patients were included in the transition phase (initiation of XEPLION treatment). Of these, 681 (80%) stabilised patients were included in the maintenance phase, then 410 (60%) in the double-blind, relapse-prevention phase.

During the maintenance phase, the doses of XEPLION were 100 mg for 69% of patients, 50 mg for 28% of patients and 25 mg for 2% of patients.

The population of the intermediate analysis included 312 patients.

The time to first relapse was longer in the XEPLION arm than in the placebo arm (p<0.001 based on the log-rank test; see figure 2).

In all, 53 patients (34%) in the placebo arm and 15 patients (10%) in the XEPLION arm had a relapse.

The relapses were mainly 25% increases in the PANSS score since randomisation (see table 4).

**Table 4. Distribution of frequency by type of relapse - intention-to-treat population**

<table>
<thead>
<tr>
<th>Type of relapse</th>
<th>Placebo n = 154</th>
<th>XEPLION n = 153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric hospitalisation</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>PANSS</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>25% increase</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>10-point increase</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Self-inflicted injury, violent behaviour</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideas or homicide</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>PANSS P1, P2, P3, P6, P7, G8</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Score ≥5 for 2 days</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Score ≥6 for 2 days</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
3.2.2. Study versus RISPERDALCONSTA LP (PSY-3002)

a) Methodology

Study PSY-3002 is a 53-week, randomised, double-blind, comparative study versus RISPERDALCONSTA LP in adults with schizophrenia.

The main objective was to demonstrate the non-inferiority of XEPLION compared with RISPERDALCONSTA LP in the treatment of schizophrenia symptoms.

The patients included were adults with schizophrenia (DSM-IV) for at least one year with a total PANSS score of between 60 and 120 on inclusion.

The patients were randomised to receive XEPLION or RISPERDALCONSTA LP at flexible doses:
- XEPLION administered (injection in the gluteal muscle) at doses of 50 mg on days 1 and 8, 25 to 75 mg on day 36 and 25 to 100 mg every four weeks thereafter;
- RISPERDALCONSTA LP administered (injection into the gluteal muscle) at doses of 25 mg on days 8 and 22, then 25 to 50 mg every two weeks; oral risperidone at a dose of 1 to 6 mg per day was combined during the first 28 days, then at a dose of 1 to 4 mg per day for a maximum 21 days following the increase in the dose of RISPERDALCONSTA LP.

The main criterion was the change in the total score on the PANSS scale since inclusion. To demonstrate non-inferiority, the lower limit of the unilateral confidence interval at 97.5% had to be higher than -5 points.

The main secondary criteria were the progression of the scores on the PANSS, CGI-S and PSP scales and the percentage of responders (response being defined as an improvement on the PANSS total score of 30% or more).

b) Results

In all, 749 patients were randomised. In the per-protocol population (570 patients), the percentage of early discontinuation was 50% in the XEPLION arm and 39% in the RISPERDALCONSTA LP arm. The reasons for discontinuation are set out in the table 5.

<table>
<thead>
<tr>
<th></th>
<th>XEPLION n = 288</th>
<th>RISPERDALCONSTA LP n = 282</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature discontinuation, n (%)</td>
<td>143 (50)</td>
<td>172 (39)</td>
</tr>
<tr>
<td>Cause of discontinuation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>66 (23)</td>
<td>34 (12)</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>46 (16)</td>
<td>45 (16)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>13 (5)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>11 (4)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

The mean dose of XEPLION was 66 mg during the study and the mean final dose was 77 mg. The mean dose of RISPERDALCONSTA LP was 33 mg during the study and the mean final dose was 36 mg.

The difference between XEPLION and RISPERDALCONSTA LP in the change in the total PANSS score was -2.6 (95% CI [-5.84; -0.61]). The lower limit of the confidence interval exceeds the predefined margin of non-inferiority by -5 points. The non-inferiority of XEPLION compared with RISPERDALCONSTA LP is therefore not demonstrated in this study.
Nor did an analysis of the data in the intention-to-treat population conclude in favour of the non-inferiority of XEPLION compared with RISPERDALCONSTA LP (difference : -3.8; 95% CI [-6.96; -0.74]). There was no difference between the XEPLION and RISPERDALCONSTA LP arms in the progression of the PSP score. The reduction in severity on the CGI-S scale was superior in the RISPERDALCONSTA LP arm to that of the XEPLION arm. The responder rate (improvement ≥ 30% on the total PANSS score) was 44% in the XEPLION arm and 54% in the RISPERDALCONSTA LP arm (relative risk= 0.8; 95% CI [0.70; 0.95]).

Table 6. Change in the total score of the PANSS scale compared with inclusion in study PSY-3002 (per-protocol population-LOCF)

<table>
<thead>
<tr>
<th></th>
<th>XEPLION (n = 389)</th>
<th>RISPERDALCONSTA LP (n = 376)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in the total PANSS score (PP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PANSS score on inclusion, mean (SD)</td>
<td>82.1 (12.35)</td>
<td>81.3 (13.01)</td>
<td></td>
</tr>
<tr>
<td>Total PANSS score at the end of the study, mean (SD)</td>
<td>70.5 (21.36)</td>
<td>67.0 (21.30)</td>
<td></td>
</tr>
<tr>
<td>Change in the total PANSS score since inclusion, mean (SD)</td>
<td>-11.6 (21.22)</td>
<td>-14.4 (19.76)</td>
<td>-2.6 [-5.84; 0.61]</td>
</tr>
<tr>
<td>Change in the PSP score since inclusion (ITT), mean (SD)</td>
<td>3.7 (16.39)</td>
<td>5.2 (15.13)</td>
<td>1.7 [-0.61; 3.97]</td>
</tr>
<tr>
<td>Change in the CGI-S score since inclusion (ITT), mean (SD)</td>
<td>-0.4 (1.25)</td>
<td>-0.6 (1.24)</td>
<td>-0.2 [-0.41; 0.006]</td>
</tr>
</tbody>
</table>

ITT : intention-to-treat; PP : per protocol

3.3. Adverse effects

In all, 3 817 patients were exposed to XEPLION in the clinical studies on schizophrenia treatment.

The adverse effects most frequently reported in the clinical studies were: insomnia, headache, weight loss, injection site reactions, feeling agitated, sleepiness, akathisia, nausea, constipation, feeling dizzy, tremors, vomiting, upper respiratory infection, diarrhoea and tachycardia. Of these adverse effects, akathisia appeared to be dose-dependent (see SPC).

Studies PSY-3003, PSY-3004 and PSY-3007

In studies PSY-3003, PSY-3004 and PSY-3007, the percentage of patients who presented with an adverse event was 60% to 83% in the XEPLION 25 to 150 mg arms and 65% to 74% in the placebo arm.

The most common adverse events (≥ 5%) were: insomnia, headache, feeling agitated, sleepiness/sedation, nausea, injection site pain, akathisia and vomiting.

The percentages of events reported were similar overall between the XEPLION and placebo arms except for weight gain (2.3% versus 0.8%) and injection site reactions (8.0% versus 2.9%) (see table 7).

Table 7. Frequency of the adverse events targeted in the comparative studies versus placebo\(^8\) (N = 1 293)

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>XEPLION</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperprolactinaemia</td>
<td>13 (1.0)</td>
<td>4 (0.8)</td>
<td>1.3 (0.4; 5.4)</td>
</tr>
<tr>
<td>Prolongation of the QT interval</td>
<td>13 (1.0)</td>
<td>5 (1.0)</td>
<td>1.0 (0.3; 3.7)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>EPS/ tardive dyskinesia</td>
<td>138 (10.7)</td>
<td>46 (9.0)</td>
<td>1.2 (0.8; 1.8)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>11 (0.9)</td>
<td>7 (1.4)</td>
<td>0.6 (0.2; 1.9)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>30 (2.3)</td>
<td>4 (0.8)</td>
<td>3.9 (1.1; 11.8)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>0.4 (0.0; 31.0)</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>68 (5.3)</td>
<td>18 (3.5)</td>
<td>1.5 (0.9; 2.7)</td>
</tr>
</tbody>
</table>

\(^8\) Studies SCH-201, PSY-3003, PSY-3004 and PSY-3007
Study PSY-3006
The percentage of patients who had an adverse event was similar in the XEPLION arm (58%) and RISPERDALCONSTA LP (53%) arm. The most common adverse events (≥ 5%) were: insomnia, sleepiness/sedation, injection site pain in the XEPLION arm and insomnia and headache in the RISPERDALCONSTA LP arm.

Study PSY-3001
The percentage of stabilised patients who had an adverse event during the double-blind phase was similar in the XEPLION arm and the placebo arm (44% versus 45%). The percentage of adverse events reported was similar overall between the groups except for weight gain: in the XEPLION arm, 7% of the patients reported weight gain as an adverse event versus 1% in the placebo arm.

Study PSY-3002
The percentage of patients who had an adverse event was similar in the XEPLION arm and the RISPERDALCONSTA LP arm (76% versus 79%).

- **Injection site reaction**
The adverse effect linked with the injection site most frequently reported in the clinical studies was pain. The majority of these reactions were reported as being of light to moderate severity. The other injection site reactions were mainly of low intensity and included hardening (common), pruritus (uncommon) and nodule (rare) (see SPC).
In studies PSY-3003 and PSY-3004, the percentages of hardening and swelling were similar between the XEPLION arm and the placebo arm (1%).
In study PSY-3007 during which an initiation dose (150 mg) was injected in the deltoid muscle, injection site pain was more common in the XEPLION arm (8%) than in the placebo arm (4%).
In study PSY-3006, the adverse events at the injection site were more common in the XEPLION arm than in the RISPERDALCONSTA LP arm: injection site pain (5.1% versus 0.8%), injection site hardening (1.5% versus 0.3%) and swelling at the injection site (1.0% vs 0.2%). None of these adverse effects was serious or led to discontinuation of the study; most were of light to moderate severity.
In studies PSY-3002, PSY-3006 and PSY-3008, the scores for pain, redness, hardening and swelling at the injection site were generally similar between the XEPLION arm and RISPERDALCONSTA LP arm.

- **Weight gain**
In studies PSY-3003 and PSY-3004 at 13 weeks, increase in weight of more than 7% (considered to be clinically significant) was more frequent in the XEPLION arm (between 4 and 12%) than in the placebo arm (2%).
In the 13-week study PSY-3007 (starting dose of 150 mg), the percentage of patients who gained over 7% in weight revealed a dose-dependent tendency, with an incidence percentage of 5% in the placebo arm compared with percentages of 6%, 8% and 13% in the XEPLION 25 mg, 100 mg and 150 mg arms respectively.
In the long-term, in study PSY-3001, during the 33-week open transition/maintenance period, 12% of the patients treated with XEPLION gained more than 7% in weight. In study PSY-3002 at 52 weeks, the percentage of patients with weight gain of more than 7% was similar between the XEPLION and RISPERDALCONSTA LP arms (14% versus 15%).

- **Extrapyramidal symptoms**
The incidence of extrapyramidal symptoms (EPS) was similar in the XEPLION and placebo arms in studies PSY-3003, PSY-3004 and PSY-3007 (10 to 12% except for the XEPLION 150 mg arm: incidence of EPS 20%).
6 cases of tardive dyskinesia were reported during the studies.
In study PSY-3002, the incidence of EPS was similar between the XEPLION arm and the RISPERDALCONSTA LP arm (parkinsonism: 12% versus 14%; akathisia: 6% versus 7%; dyskinesia: 4% versus 3%). It was the same case in study PSY-3006 (parkinsonism: 8% versus 8%; akathisia: 3% versus 3%; dyskinesia: 2% versus 2%).

3.4. Conclusion

Short-term efficacy data
XEPLION short-term efficacy was evaluated in four studies:
- Three 13-week comparative studies versus placebo (PSY-3003, PSY-3004, PSY-3007): XEPLION administered in fixed doses was more efficacious than placebo in improving schizophrenia symptoms whatever the dose administered (25 mg, 50 mg, 100 mg or 150 mg) in studies PSY-3004 and PSY-3007. In PSY-3003, only the XEPLION 100 mg arm showed higher efficacy than placebo.
- One 13-week comparative study versus RISPERDALCONSTA LP (PSY-3006): this study concluded in favour of the non-inferiority of XEPLION administered according to the regimen in the Marketing Authorisation (150 mg on day 1, 100 mg on J8 in the deltoid muscle, then flexible monthly doses thereafter) compared with RISPERDALCONSTA LP in improving the PANSS score.

These four studies were carried out in order to obtain a Marketing Authorisation for the treatment of adult schizophrenia, including treatment of the acute phase of schizophrenia. Long acting injectable antipsychotics are usually intended for maintenance treatment of schizophrenia in stabilised patients. The use of a long acting injectable antipsychotic without prior stabilisation with an oral treatment should remain an exceptional situation since it does not allow dose adjustment and has risks in terms of tolerability. XEPLION has obtained a Marketing Authorisation for treatment of schizophrenia without prior stabilisation with an oral treatment in a restricted group of patients: “in selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long acting injectable treatment is needed”.

The benefit of XEPLION in treatment of the acute phase of schizophrenia without prior stabilisation with an oral treatment still has to be determined taking into account:
- the reservations on the use of long acting injectable antipsychotics in non-stabilised patients (no dose flexibility, risks in terms of tolerability),
- the difficulty in determining the group of patients likely to benefit from XEPLION in the absence of a precise definition of the concepts "prior response", "light to moderate symptoms" and "need" for long acting injectable treatment.

Long-term efficacy data
Data on XEPLION efficacy in the maintenance treatment of schizophrenia are based on two studies:
- A 52-week comparative study versus placebo (PSY-3001) on preventing schizophrenic relapses which was stopped at the end of an intermediate analysis showing that...
XEPLION was superior to placebo in the time-to-relapse in patients previously stabilised under this treatment.

- A 53-week comparative study versus RISPERDALCONSTA LP (PSY-3002) which did not conclude in favour of the non-inferiority of XEPLION compared with RISPERDALCONSTA LP in improving the PANSS score. In this study, the dose of XEPLION administered on day 1 and day 8 was 50 mg, which is lower than the dose recommended in the Marketing Authorisation (150 mg on day 1 and 100 mg on day 8).

The Transparency Committee regrets that the dose regimen recommended in the Marketing Authorisation has not been evaluated in maintenance treatment of schizophrenia in patients stabilised with oral risperidone or paliperidone. It also regrets the absence of a study evaluating XEPLION in relapse prevention compared with an active treatment. It should be noted that oral paliperidone is not available in France.

**Tolerability data**

The tolerability data from the clinical studies are consistent with the known adverse effects profile of oral paliperidone and the other antipsychotics.

The adverse effects most frequently reported in the clinical studies were: insomnia, headache, weight gain, injection site reactions, feeling agitated, sleepiness, akathisia, nausea, constipation, feeling dizzy, tremors, vomiting, upper respiratory infection, diarrhoea and tachycardia. Of these adverse effects, akathisia appeared to be dose-dependent (see SPC).

The injection site adverse effect most frequently reported in the clinical studies was pain. The majority of these reactions were reported as being of light to moderate severity.
4.1. **Actual benefit**

The basic characteristics of schizophrenia are a series of signs and symptoms referred to as “positive” (delusions, hallucinations, disordered speech, grossly disorganised or catatonic behaviour) or “negative” (blunted affect, alogia, lack of volition) combined with clear social dysfunction and dysfunctional activity. Schizophrenia progression is variable: some patients have exacerbation and remission, whilst others are chronically affected. Some patients seem to have relatively stable progression, whilst others have progressive aggravation combined with severe incapacity.

XEPLION is a maintenance treatment of schizophrenia in adult patients stabilised with paliperidone (not available in France) or risperidone. According to the Marketing Authorisation, XEPLION may be used without prior stabilisation with an oral treatment in a restricted group of patients (in selected adult patients with schizophrenia who previously responded to oral paliperidone or risperidone, if the psychotic symptoms are light to moderate and if a long acting injectable treatment is necessary). The efficacy/adverse effects ratio of XEPLION is high. The drug alternatives are all of the antipsychotics.

**Public health benefit:**

The public health burden represented by schizophrenic psychoses, taking into account their frequency and seriousness, is substantial. Their improved treatment is a public health requirement consistent with established priorities (Public Health Act 2004\(^{13}\), GTNDO\(^{14}\)).

In the light of the trial data available (particularly non-inferiority versus RISPERDALCONSTA LP not demonstrated), it is not expected that the medicinal product XEPLION will benefit morbidity and quality of life compared with existing therapies.

In spite of the better theoretical practicality of this particular injectable form of risperidone LP, the medicinal product XEPLION would therefore not be able to provide an additional response to the identified public health requirement. Consequently, in the current state of knowledge and taking into account other therapies available, it is not expected that the medicinal product XEPLION will benefit public health in this indication.

In the maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone:

The Transparency Committee regrets that the dose regimen recommended in the Marketing Authorisation has not been evaluated in patients stabilised with oral risperidone or paliperidone. It also regrets the absence of a study evaluating XEPLION in relapse prevention compared with an active treatment.

The results of study PSY-3002 at 53 weeks are negative but the administration regimen of the product in this study (dosage and injection site) does not correspond to that finally adopted in the Marketing Authorisation.

\(^{13}\) Public Health Act 2004- 806 of 9 August 2004 : Objective on neuropsychiatric disorders

\(^{14}\) GTNDO = National Technical Group Defining Objectives (DGS- 2003)
Taking into account also:

- the demonstration of its higher efficacy than placebo in the prevention of schizophrenic relapses in stabilised patients (study PSY-3001),
- the demonstration of non-inferiority of XEPLION compared with RISPERDALCONSTA LP in the symptomatic control of schizophrenia at 13 weeks (study PSY-3006),

the actual benefit of XEPLION is **substantial** in the maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.

In the treatment of schizophrenia without prior stabilisation with an oral treatment\(^\text{15}\):

In the current state of knowledge and practices, taking into account:

- the reservations on the use of long acting antipsychotics in non-stabilised patients (no dose flexibility, risks in terms of tolerability),
- the difficulty in determining the group of patients likely to benefit from XEPLION in the absence of a precise definition of the concepts "prior response", "light to moderate symptoms" and "need" for long acting injectable treatment.

the actual benefit of XEPLION is **insufficient** in the treatment of schizophrenia without prior stabilisation with an oral treatment\(^\text{15}\).

### 4.2. Improvement in actual benefit

The Transparency Committee recognises the benefit of the administration properties of XEPLION (monthly administration, no oral supplementation on initiation of the treatment, packaging in pre-filled syringes, no refrigeration necessary) compared with RISPERDALCONSTA LP.

However, the Transparency Committee regrets that the dose regimen recommended in the Marketing Authorisation has not been evaluated in the maintenance treatment of schizophrenia in patients stabilised with oral risperidone or paliperidone. It also regrets the absence of a study evaluating XEPLION in relapse prevention compared with an active treatment.

Consequently, XEPLION does not bring any improvement in actual benefit (IAB V) in the maintenance treatment of adult patients stabilised with paliperidone or risperidone.

### 4.3. Therapeutic use\(^\text{16,17,18}\)

Antipsychotics are the pharmacological reference treatment of schizophrenia. The prescription of a long acting injectable form may be envisaged in a context of combined therapy in a stabilised patient.

XEPLION is a therapeutic alternative to the other long acting injectable antipsychotics indicated in the maintenance treatment of schizophrenia in patients stabilised with oral risperidone.

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\(^{15}\) Indication in the Marketing Authorisation: “in selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long acting injectable treatment is needed”


http://www.has-sante.fr/portail/upload/docs/application/pdf/guide_ald23_schizophr_juin_07.pdf
4.4. Target population

According to the European Brain Council\(^{19}\), approximately 300,000 people suffer from schizophrenia in France.

4.5. Transparency Committee recommendations

The **Transparency Committee recommends** inclusion of XEPLION on the list of the medicinal products refundable by National Health Insurance and on the list of the medicines approved for hospital use and various public services in the following indication: “maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone ».

The **Transparency Committee does not recommend** inclusion of XEPLION on the list of the medicinal products refundable by National Health Insurance and on the list of the medicines approved for hospital use and various public services in the following indication: “in selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long acting injectable treatment is needed”.