HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 September 2009

ZYPADHERA 210 mg, powder and solvent for prolonged-release suspension for injection
Vial (CIP: 34009 574 691 6 0)

ZYPADHERA 300 mg, powder and solvent for prolonged-release suspension for injection
Vial (CIP: 34009 574 692 2 1)

ZYPADHERA 405 mg, powder and solvent for prolonged-release suspension for injection
Vial (CIP: 34009 574 693 9 9)

Applicant: LILLY France

Olanzapine pamoate monohydrate
ATC code: N05AH03

List I
Medication reserved for hospital use.
Prescription reserved for specialists in psychiatry.

Date of marketing authorisation (centralised procedure): 19 November 2008

Reason for request: inclusion on the list of medicines approved for use in hospitals.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICATION

1.1. Active substance

Olanzapine pamoate monohydrate

1.2. Indication

Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

1.3. Dosage

"FOR INTRAMUSCULAR USE ONLY. DO NOT ADMINISTER INTRAVENOUSLY OR SUBCUTANEOUSLY.

ZYPADHERA should only be administered by deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique and in locations where post-injection observation and access to appropriate medical care in the case of overdose can be assured.

After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose. It should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until clinical examination indicates that signs and symptoms have resolved.

Patients should be treated initially with oral olanzapine before administering ZYPADHERA, to establish tolerability and response to treatment."

"In order to identify the first ZYPADHERA dose for all patients the scheme in Table 1 should be considered.

Table 1. Recommended dose scheme between oral olanzapine and ZYPADHERA

Target oral dose	Recommended starting dose	Maintenance dose after 2 months of treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

Dose adjustment

Patients should be monitored carefully for signs of relapse during the first one to two months of treatment. During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period. During treatment, dose may subsequently be adjusted on the basis of individual clinical status. After clinical reassessment dose may be adjusted within the range 150 mg to 300 mg every 2 weeks or 300 to 405 mg every 4 weeks.

(Table 1).

Supplementation
Supplementation with oral olanzapine was not authorised in double-blind clinical trials. If oral olanzapine supplementation is clinically indicated, then the combined total dose of olanzapine from both formulations should not exceed the corresponding maximum oral olanzapine dose of 20 mg/day.

Switching to other antipsychotic medicinal products
There are no systematically collected data to specifically address switching patients from ZYPADHERA to other antipsychotic medicinal products. Due to the slow dissolution of the olanzapine pamoate salt which provides a slow continuous release of olanzapine that is complete approximately six to eight months after the last injection, supervision by a clinician, especially during the first 2 months after discontinuation of ZYPADHERA is needed when switching to another antipsychotic product, and is considered medically appropriate.

Elderly patients
ZYPADHERA has not been systematically studied in elderly patients (> 65 ans).
ZYPADHERA is not recommended for treatment in the elderly population unless a well-tolerated and effective dose regimen using oral olanzapine has been established. A lower starting dose (150 mg every 4 weeks) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant. It is not advisable to initiate ZYPADHERA in patients > 75 years.

Patients with renal and/or hepatic impairment
Unless a well-tolerated and effective dose regimen using oral olanzapine has been established in such patients, ZYPADHERA should not be used. A lower starting dose (150 mg every 4 weeks) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh class A or B), the starting dose should be 150 mg every 4 weeks and only increased with caution.

1.4. Special warnings and precautions for use

"Special care must be taken to apply appropriate injection techniques to avoid inadvertent intravascular or subcutaneous injection.

Use in patients who are in an acutely agitated or severely psychotic state
ZYPADHERA should not be used to treat patients with schizophrenia who are in an acutely agitately or severely psychotic state such that immediate symptom control is warranted.

Post-injection syndrome

During pre-marketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of ZYPADHERA. These reactions occurred in less than 0.1% of injections and approximately 1.4 % of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion. In most cases, initial signs and symptoms related to this reaction have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 – 72 hours after injection. Reactions occurred rarely (<1 in 1,000 injections) between 1 and 3 hours, and very rarely (<1 in 10,000 injections) after 3 hours. Patients should be advised about this potential risk and the need to be observed for 3 hours in a healthcare facility each time ZYPADHERA is administered.

Prior to giving the injection, the healthcare professional should determine that the patient will not travel alone to their destination. After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

It should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until clinical examination indicates that signs and symptoms have resolved.

For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse effects, be able to obtain assistance if needed, and should not drive or operate machinery."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N	Nervous system
N05	Psycholeptics
N05A	Antipsychotics
N05AH	Diazepines, oxazepines and thiazepines
N05AH03	Olanzapine

2.2. Medicines in the same therapeutic category

HALDOL DECANOAS, solution for injection
SEMAP, tablet

RISPERDALCONSTA LP, suspension for injection

MODECATE, solution for injection
PIPORTIL L4, solution for injection
TRILIFAN Retard, solution for injection

FLUANXOL LP, solution for injection

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier submitted mentions two comparative, randomised, double-blind studies:
- a superiority study evaluating the efficacy of olanzapine pamoate (OP) 210 mg/2 weeks, 300 mg/2 weeks and 405 mg/4 weeks versus placebo in treatment of the acute psychotic episode (HGJZ study). This study does not fulfil the indication of the product but has evaluated in schizophrenic patients the dosage of 210 mg/2 weeks, a dose not studied in maintenance treatment.
- a non-inferiority study evaluating the efficacy of OP (150 mg/2 weeks or 300 mg/2 weeks) versus oral olanzapine in maintenance treatment in patients stabilised on oral olanzapine (HGKA study).

Interim results of a 3-year tolerability follow-up in patients treated with OP were presented.

3.1.1 Acute psychotic episode

The HGJZ study, a randomised, double-blind superiority study compared the efficacy and tolerability of olanzapine pamoate with the one of placebo in the treatment of acute psychosis in patients with schizophrenia according to the DSM-IV or DSM-IV-TR[1] criteria.

At inclusion, the patients were hospitalised for an acute psychotic episode and had a total BPRS[2] score of ≥ 48.

The primary efficacy criterion was the change from baseline of the total PANSS[3] score after 8 weeks of treatment.
Among the secondary criteria, the percentage of responders was evaluated (decrease ≥ 40% in total PANSS score).
A total of 404 patients, mean age 41 years, was randomised in four groups: placebo/2 weeks (n=98), OP 210 mg/2 weeks (n=106), OP 300 mg/2 weeks (n=100), OP 405 mg/4 weeks (n=100).
At least two acute psychotic episodes have been reported in the 2 years in 71% of patients; 94% of patients had previously received at least one antipsychotic: risperidone (39%), olanzapine (38%), haloperidol (26%).

Initial mean PANSS scores were: 101 for the total score, 25.5 for the positive symptoms and 25 for the negative symptoms. The initial mean BPRS[4] score was 41.

Mean changes from baseline in PANSS scores at 8 weeks:

Evaluation criteria	Placebo n=98	OP 210 mg/2 weeks n=106	OP 405 mg/4 weeks n=100	OP 300 mg/2 weeks n=100
Total PANSS score	-8.5	-22.5*	-22.6*	-26.3*
Positive symptoms	-1.9	-6.3*	-7.2*	-7.4*
Negative symptoms	-2.1	-4.8*	-4.6*	-6.3*
Psychopathology	-4.4	-11.4*	-10.8*	-12.6*
Responders (%)	11	18	20	25.5

ITT analysis – LOCF; * $p < 0.001$ versus placebo

137 patients (34%) discontinued treatment before the end of the double-blind period.

1 DSM-IV or DSM-IV-TR: Manual Diagnosis and Statistics of Mental Disorders.

2 BPRS: Brief Psychiatric Rating Scale (score 0 to 108). 18 item scale: 2 to 9 and 15 to 24 of the PANSS. The severity of each symptom is rated 1 to 7.

3 PANSS: Positive And Negative Syndrome Scale (score 30 to 210). 30 item scale: Sub-scale of positive symptoms (7 items, score 7 to 49), sub-scale of negative symptoms (7 items, score 7 to 49), sub-scale of general psychopathology (16 items, score 16 to 112). The severity of each symptom is rated 1 (not present) to 7 (extremely severe).

4 The items of the BPRS scale are rated 0 to 6 in the analysis of total scores

Reasons for withdrawal:

	Placebo n=98	OP 210 mg/2 weeks n=106	OP 405 mg/4 weeks n=100	OP 300 mg/2 weeks n=100
Treatment withdrawal (%)	42 (43)	34 (32)	28 (28)	33 (33)
Inadequate response	24	12	10	13
Withdrawal of consent	9	15	12	9
adverse event	5	3	4	6
Other	4	4	2	5

The most common adverse events reported in the groups treated with olanzapine pamoate were: headache (14% vs 8% on placebo) and sedation (8% vs 2%).

3.1.2 Maintenance treatment in patients stabilised on oral olanzapine

The HGKA, randomised, double-blind non-inferiority study compared the efficacy of OP (150 mg or 300 mg) administered every 2 weeks versus oral olanzapine (10, 15 or 20 mg/day) in the prevention of psychotic episodes in outpatients with schizophrenia according to the DSM-IV or DSM-IV TR criteria. The superiority of OP 300 mg/2 weeks, 405 mg/4 weeks and 150 mg/2 weeks versus OP 45 mg/4 weeks on the time until onset of an exacerbation of symptoms at 24 weeks was also evaluated.

The primary evaluation criterion was the appearance of a psychotic episode during the 24 weeks of treatment (Kaplan Meier estimate). Exacerbation in symptoms was defined by one of the following criteria:

- worsening of one of the positive BPRS items with a score of > 4 and an increase of ≥ 2 in this item;
- worsening of one of the positive BPRS items with a score of > 4 and an increase of ≥ 4 in the score of the positive sub-scale of BPRS;
- hospitalisation for worsening of positive symptoms.

Among the secondary criteria, the PANSS and BPRS scores were evaluated.

At baseline, the patients were stabilised on oral olanzapine (10, 15 or 20 mg/day) as monotherapy for at least 4 weeks:

- fixed dose of oral olanzapine;
- a score ≤ 4 to 4 for positive items of BPRS[1] (conceptual disorganisation, suspiciousness, hallucinations, unusual thoughts);
- a CGI-I score of 1, 2, 3 or 4.

A total of 1065 patients, mean age 39 years, was randomised to five groups for a double-blind period of 24 weeks: OP 300 mg/2 weeks (n=141), OP 405 mg/4 weeks (n=318), OP 150 mg/2 weeks (n=140) versus OP 45 mg/4 weeks (n=144) or oral olanzapine 10, 15 or 20 mg/day (n=322). More than 60% of patients had previously been treated with an antipsychotic; 31% of patients had had no exacerbation in the past 24 months before their inclusion in the study, 53% of patients 1 to 2 exacerbations, 16% of patients at least 3 exacerbations.

1 BPRS : Brief Psychiatric Rating Scale (score de 0 à 108Scale on 18 items : 2 to 9 et 15 to 24 on the PANSS. The severity of each symptom is scored to 1 to 7 (0 à for the scores analysis)

753 patients completed the double-blind period (71%).
The mean dose of oral olanzapine was 14 mg/day (743 patients).

Results of intention to treat analysis:

90% of patients in the OP group (150 mg or 300 mg/2 weeks) and 93% in the oral olanzapine group (0.03 ± 0.024, IC 95%: -0.02 – 0.08, Δ non inf. 0.20) had no exacerbation in symptoms at 24 weeks. This percentage was 90% in the OP 405 mg/4 weeks group.
Time until onset of an exacerbation in symptoms at 24 weeks in patients treated with OP 300mg/2 weeks, 405mg/4 weeks and 150 mg/2 weeks was greater than that observed in the patients treated with OP 45 mg/4 weeks.
Of the patients stabilised on olanzapine 15 to 20 mg/day, the relative risk of an exacerbation in symptoms was 2.5 times greater in the OP 150 mg/2 weeks group than in the oral olanzapine group.

Mean initial PANSS scores were between 54 and 57, between 11 and 12 for positive symptoms, between 16 and 17 for negative symptoms. The mean initial RS score varied between 11.5 and 13.

Mean changes in PANSS and BPRS scores at 24 weeks (LOCF):

Treatment / Evaluation criteria	Oral olanzapine n=322	OP 150 mg/2 weeks n=140	OP 300 mg/2 weeks n=140	OP 405 mg/4 weeks n=316	OP 45 mg/4 weeks n=144
Total PANSS score	- 2.52	2.66	-2.19	-0.09	7.25
Positive symptoms	- 0.16	1.29	0.16	0.56	3.03
Negative symptoms	- 1.09	-0.06	-0.95	-0.69	0.51
BPRS	-1.10	2.29	-0.97	0.34	4.65

The changes in quality-of-life scores were not different between the treatment groups.

Concomitant administration of benzodiazepine during the study was reported in 33% of patients. An anticholinergic was used in 4.3%, 9.2%, 10.4% and 8.3% of patients respectively in the OP 150 mg/2 weeks, OP 300 mg/2 weeks, OP 405 mg/4 weeks and OP 45 mg/4 weeks groups and in 8.7% of patients in the oral olanzapine group.

A total of 312 patients (29%) discontinued the treatment before the end of the double-blind period:

	OP 45 mg/4 weeks n=144	OP 150 mg/2 weeks n=140	OP 300 mg/2 weeks n=141	OP 405 mg/4 weeks n=318	Oral olanzapine n=322
	68 (47%)	50 (36%)	34 (24%)	96 (30%)	64 (20%)
Inadequate response	2	4	2	2	4
Withdrawal of consent	10	9	12	27	20
Adverse event	6	7	4	10	8
Other	8	8	9	18	9
Re-stabilisation phase*	42 (30%)	22 (16%)	7 (5%)	39 (12%)	23 (7%)

* 133 patients who discontinued treatment due to exacerbation of symptoms were included in the open “restabilisation” phase and treated with oral olanzapine

At least one adverse event was reported in 51% of patients; a serious event was reported in 5.4% of patients.
The most commonly reported adverse events (> 5%) were: insomnia 15.3%, 7.9%, 6.4%, 7.2% and 4% respectively in the OP 45mg/4 weeks, OP 150 mg/2 weeks, OP 300 mg/2 weeks, OP 405 mg/4 weeks and oral olanzapine groups, weight gain (4.2%, 8.6%, 10.6%, 5%, 7.5%), anxiety (4.9%, 3.6%, 5%, 5.3, 2.8%), nasopharyngitis (2.1%, 5.7%, 5%, 3.5%, 4.3%), somnolence (4.9%, 5.7%, 3.5%, 3.1%, 2.8%), headache (0.7%, 5%, 2.1%, 2.8%, 4.3%).
A clinically significant weight gain (≥ 7%), which was recorded systematically, was observed in 15-21% of patients.

3.1.3 Long-term follow-up study (22 months)

On 30 June 2006, the HGKB study included 880 patients who completed one of 3 olanzapine pamoate development studies (HGJZ, HGKA or LOBS kinetic study). An initial dose of 210 mg of OP was administered to the patient in the initial two weeks then flexible doses between 45 and 405 mg every 2, 3 or 4 weeks. Additional oral olanzapine treatment was prescribed in 179 patients (20.3%).
Of the concomitant treatments, benzodiazepines were used in 31.6% of patients, anticholinergics in 8.6% of patients.

Exposure was equivalent to 586 patient-years. Follow-up was terminated prematurely in 23.4% of patients (decision of the patient in 10.3% of cases, lost to follow-up in 4%, adverse event in 3.9%). A serious adverse event was reported in 74 of patients (8.4%). Overdose was reported in 3 of these patients. The most common serious event was psychotic disorder or schizophrenia (3.2%).

4% of patients withdrew from treatment due to an adverse event. The most common events were: weight gain (0.7%) and psychotic disorders (0.5%).
At least one adverse event was reported in 446 patients (50.7%). The most common were: weight gain (7.8%), insomnia (6.5%), anxiety (5.9%), somnolence (5.7%) and headache (3.9%).
1.3% of patients suffered from pain at the injection site. Ten events (in 9 patients) were described as possibly linked to accidental intravascular injection of the product.

A raised prolactin level was observed in 25.7% of patients analysed (n=136). The mean increase in serum levels was 4.63 µg/L (n=178). Mean increases in fasting glycaemia (0.20 mmol/l), total cholesterol (0.09 mmol/l), LDL cholesterol (0.06 mmol/l) and triglycerides (0.03 mmol/l) were reported.

A clinically significant weight gain (≥ 7%), which was recorded systematically, was observed in 16.4% of patients (a decrease in 8.6% of patients).

3.2. Adverse events

A total of 1 778 patients exposed to olanzapine pamoate during development of the product was analysed. Of these patients, 445 received at least one year of ZYPADHERA treatment.
The most commonly reported adverse effects were: insomnia (10.8%), weight gain (8.4%), anxiety (7.8%), headache (7.3%), somnolence (6.7%) and pain at the injection site (5.5%).

On 30 May 2008, over 40 000 injections of olanzapine pamoate were administered to 2 054 patients during clinical studies. Symptoms compatible with overdose from olanzapine were reported in 28 patients in the course of 29 injections, i.e. approximately 0.07% of injections and 1.4% of patients. Initial signs and symptoms were observed between 5 minutes and 5 hours after injection (< 1/10 000 cases after 3 hours). In 79% of cases, these symptoms led to hospitalisation or admission to casualty, for a duration of 24 to 72 hours in 41% of cases. The symptoms resolved within 72 hours of injection.

The European Risk Management Plan includes:
- a prospective, observational study, study B034, whose objective was to determine in real use conditions the incidence and clinical presentation of all adverse events occurring within 24 hours of injection and their evolution, to classify them and to determine the potential risk factors.
- a study of the metabolic risk (study F1D-MC-S014 – study of sensitivity to insulin of schizophrenic patients treated with olanzapine or risperidone).

3.3. Conclusion

The HGKA study evaluated ZYPADHERA in the prevention of psychotic episodes in patients stabilised on oral olanzapine. The percentage of patients who presented no exacerbation in symptoms at week 24 of treatment with OP 150 mg/2 weeks or 300 mg/2 weeks was not inferior to that observed in the 10 to 20 mg/day oral olanzapine group. The time until onset of an exacerbation in symptoms observed with OP 150 mg/2 weeks, 300 mg/2 weeks and 405 mg/4 weeks was greater than that observed with OP 45 mg/4 weeks. There was a greater percentage of treatment withdrawals due to exacerbation of symptoms in the OP 150 mg/2 weeks group than in the oral olanzapine group (16% *vs* 7%).
Efficacy of ZYPADHERA at the 210 mg/2 weeks dose was not evaluated.

The HGJZ study compared olanzapine pamoate (210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks) to placebo in patients with one acute psychotic episode. Mean changes in PANSS scores observed at 8 weeks on olanzapine pamoate were between -22.5 and -26.3, compared with -8.5 for placebo. 31% of patients treated with OP withdrew prematurely from treatment, compared with 43% in the placebo group.

Considering the risk of post-injection syndrome and the resultant monitoring required, use of ZYPADHERA was restricted in the hospital environment. A plan is currently being drawn up to minimise these risks and includes in particular a training programme to make healthcare professionals aware of what conditions are necessary when prescribing the product.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The main characteristics of schizophrenia are the presence of a group of so-called positive signs and symptoms (delirious ideas, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour) or negative signs and symptoms (affective blunting, alogia, disturbance of volition) associated with clear social dysfunction or disturbance in activities.
Schizophrenia evolves differently in different patients. Some patients present with exacerbations and remissions, whereas others remain chronically affected. Some patients appear to have a relatively stable evolution, while others present with a progressive deterioration associated with severe incapacity.

ZYPADHERA is a maintenance treatment in adult schizophrenic patients stabilised on oral olanzapine.
Considering the risk of post-injection syndrome, the efficacy/adverse effects ratio of these medicinal products is modest.

Public health benefit:

Given the frequency and severity of schizophrenia, its burden in terms of public health is significant.
Improving the management of schizophrenia is still a public health priority (GTNDO[1] requirement).
Considering the available data (non inferiority study versus oral olanzapine), no additional effect on morbidity or mortality is expected from the medicinal product ZYPADHERA.
Administration of ZYPADHERA (intramuscular route) requires additional medical surveillance compared with other injectable prolonged-release antipsychotics, which may have a negative impact on the healthcare system.
The available data do not support the assumption that the medicinal product ZYPADHERA can fulfil the need of improving the management of adult schizophrenic patients stabilised on oral olanzapine in whom adherence is difficult.
As a result, the medicinal product ZYPADHERA is not expected to provide a public health benefit.

There are therapeutic alternatives to these medicinal products.

Therefore the actual benefit provided by ZYPADHERA in this indication is moderate.

4.2. Improvement in actual benefit

ZYPADHERA do not provide any improvement in the actual benefit (IAB V) in the management of schizophrenic patients. This prolonged-release formulation represents an alternative treatment to maintenance treatment with oral olanzapine.

1 Groupe Technique National de Définition des Objectifs (DGS-2003) (National Technical Group for Defining Public Health Objectives)

4.3. Therapeutic use[1,2,3,4,5]

Neuroleptics have proven efficacy in the treatment of schizophrenic patients, and in particular on the positive symptoms.
Two thirds to three quarters of patients will suffer from side-effects from these treatments during their life-time (psychological effects, neurological effects, vegetative effects, endocrine effects).
Second-generation antipsychotics are certainly not without adverse effects but they can be recommended as first-line treatment in newly-diagnosed schizophrenics, mainly because there is a smaller risk of acute extra-pyramidal side-effects at the dosages defined by the marketing authorisation. First-generation antipsychotics are indicated in stabilised patients who do not have major side-effects.
Whichever antipsychotic is used, the dose must be adjusted to limit the onset of adverse effects (neurological, cardiovascular, metabolic, endocrine).

Antipsychotic monotherapy should be favoured. Prescription of a prolonged-action formulation can be considered in the context of combined therapy in a stabilised patient.

A multi-dimensional approach is required in patients suffering from schizophrenia. The drug treatments will be combined with individual or group psychotherapy, management by institutions or families, and social interventions.

4.4. Target population

Between 300 000 and 500 000 adults in France suffer from chronic delirious psychosis, 200 000 to 250 000 suffer from schizophrenia.
It is not possible to specify the population of patients stabilised on oral olanzapine who could benefit from this prolonged-release formulation.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicinal products approved for use by hospitals and various public services in the indication and at the dosages in the marketing authorisation.

Considering the risk of post-injection syndrome described in the SPC, administration of ZYPADHERA should be reserved for hospital departments specialising in psychiatry, which excludes part-time medico-psychological centres and healthcare centres.

The Transparency Committee wishes to have at its disposal the results of a study monitoring schizophrenic patients treated in France with ZYPADHERA. The objectives of this study must be documented in a real treatment situation:

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1 National Institute for Clinical Excellence. 2002. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. Technological Appraisal Guidance N°. 43, London, www.nice.org.uk.

2 Schizophrénies débutantes: diagnostic et modalités thérapeutiques - Conférence de consensus ANAES, 23-24 janvier 2003.

(Newly-diagnosed schizophrenia: diagnosis and therapeutic methods - ANAES consensus conference 23-24 Jan 2003)

3 American Psychiatric Association. 2004. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Am J Psychiatry 161(Suppl 2):1-114.

4 World Federation of Societies of Biological Psychiatry (WFSBP). Guidelines for Biological Treatment of Schizophrenia, Part 2: Long-term treatment of schizophrenia. The World Journal of Biological Psychiatry, 2006;7(1):5-40.

5 Dollfus S. Les antipsychotiques lors d'un premier épisode psychotique. Annales Médico-Psychologiques 167 (2009) 86-92.

(Antipsychotics for use in an initial psychotic episode)

- the characteristics of the patients treated: sex, age, socio-professional category, history of the illness,
- the characteristics of the prescribers, the use of healthcare and healthcare services (place of administration and method of follow-up and medical surveillance),
- methods for prescribing and using ZYPADHERA: dosage, duration of treatment, premature withdrawals with reasons and associated treatments,
- a description of the post-injection syndrome, their frequency and management.

In the event that the studies planned or ongoing, especially in the context of the European Risk Management Plan, do not answer the questions of the Transparency Committee, a specific study must be performed.
The duration of the study should be justified by an independent scientific committee.

Packaging:

Packaging of the dosages presented (one vial of powder and one vial of solvent per box) is adjusted to the dosages 210 mg/2 weeks, 300 mg/2 weeks, 300 mg/4 weeks and 405 mg/4 weeks.
However, situations where the dosages 150 mg/2 weeks or 150 mg/4 weeks are specified by the marketing authorisation would justify making a dosage of 150 mg available.