HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
28 May 2014

ADASUVE 9.1 mg, inhalation powder, pre-dispensed
B/5 (CIP: 3400958597671)

Applicant: BIOPROJET PHARMA

INN	loxapine
ATC code	N05AH01 (antipsychotic)
Reason for the request	**Inclusion**
List concerned	**Hospital use (French Social Security Code L.5123-2)**
Indication concerned	**"Rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**ADASUVE does not provide any improvement in actual benefit (level V, non-existent) in the rapid control of mild to moderate agitation in adult patients with schizophrenia or bipolar disorder.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	20/02/2013
Prescribing and dispensing conditions/special status	List I

ATC Classification	N05	Psycholeptics
	N05A	Antipsychotics
	N05AH	Diazepines, oxazepines, thiazepines, and oxepines
	N05AH01	loxapine

02 BACKGROUND

This is a request for inclusion of ADASUVE on the list of medicinal products approved for hospital use. ADASUVE is a proprietary medicinal product containing loxapine, administered by inhalation, for the rapid control of mild to moderate agitation in adult patients with schizophrenia or bipolar disorder.
Loxapine is an antipsychotic that has been on the market for around thirty years under the name LOXAPAC. It is available in tablet form and as an oral solution for the treatment of schizophrenia and as a solution for intramuscular injection for the treatment of states of agitation and aggressiveness during psychotic states.

03 THERAPEUTIC INDICATION

“ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder.
Patients should receive regular treatment immediately after control of acute agitation symptoms.”

04 DOSAGE

“ADASUVE should only be administered in a hospital-setting under the supervision of a healthcare professional.
Short-acting beta-agonist bronchodilator treatment should be available for treatment of possible severe respiratory side-effects (bronchospasm).
The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.
A lower dose of 4.5 mg may be given if the 9.1 mg dose was not previously tolerated by the patient or if the physician decides a lower dose is more appropriate.
Patient should be observed during the first hour after each dose for signs and symptoms of bronchospasm.”
Please refer to the SPC for more detailed information.

05 THERAPEUTIC NEED

Agitation is a psychomotor behavioural disorder characterised by motor hyperactivity accompanied by loss of control over actions, speech, and thought.[1] Psychiatric illnesses (manic episodes, schizophrenia, delirious episodes, panic attacks, etc.) are most commonly the cause.
Management should be prompt in order to prevent escalation to violence and the subject turning to auto- or hetero-aggressive behaviour. It relies in the first instance on a relational approach (moving the subject to a quiet location and encouraging verbalisation). Medicinal treatment should be used only as a last resort, in the event of failure of the relational approach. The medicines used are primarily antipsychotics and/or benzodiazepines administered either orally or by intramuscular injection.
There have been only a few randomised studies that evaluated the efficacy and safety of these products in the treatment of agitation.[2] Their use relies principally on empirical findings.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

If the relational approach should fail, antipsychotics and/or benzodiazepines, given either orally – always the preferred route – or parenterally, are used in current practice.

The only products to have Marketing Authorisation in adults in the treatment of agitation in psychotic states are antipsychotics administered by the intramuscular route:
- aripiprazole (ABILIFY);
- amisulpride (SOLIAN);
- chlorpromazine (LARGACTIL);
- cyamemazine (TERCIAN);
- haloperidol (HALDOL);
- levomepromazine (NOZINAN);
- loxapine (LOXAPAC);
- olanzapine (ZYPREXA);
- tiapride (TIAPRIDAL).

◗ Conclusion

Clinically relevant comparators of ADASUVE are the orally or parenterally administered antipsychotics or benzodiazepines used in the treatment of agitation of psychiatric aetiology.
The only products to have Marketing Authorisation in these states of agitation are intramuscular antipsychotics.

07 ANALYSIS OF AVAILABLE DATA

[1] ANAES [National Health Accreditation and Assessment Agency]. [Conférence de Consensus : « L'agitation en urgence (petit enfance excepté) ».] JEUR 2003; 16: 58-64.
[2] NICE. Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments. Clinical Guideline 25. February 2005. www.nice.org.uk.

07.1 Efficacy

The company's dossier is based on two randomised double-blind studies comparing the efficacy and safety of ADASUVE with that of placebo in patients with acute agitation:
- in patients with schizophrenia (study 004-301);
- in patients with manic episodes in bipolar disorder (study 004-302).

7.1.1 Study design

Studies 004-301 and 004-302 are based on identical protocols.
These were two double-blind, randomised, multicentre superiority studies versus placebo. The two studies were conducted exclusively in the United States.

The primary objective was to evaluate the efficacy and safety of inhaled loxapine, compared with placebo, for the control of acute agitation in patients with schizophrenia (study 004-301) or manic episodes in bipolar disorder (study 004-302).

The inclusion criteria were as follows:
- Age between 18 and 55 years;
- Diagnosis of schizophrenia (DSM IV criteria) in study 004-301 or a diagnosis of manic or mixed episodes in bipolar I disorder (DSM IV criteria) in study 004-302;
- Presenting a state of agitation with a total score ≥ 14 on the PANSS-EC[3] agitation scale and a score ≥ 4 on at least one of the five items in this scale;
- Able to give written consent to participation in the study.

Patients were recruited from among: a) patients admitted to hospital or to a research unit with a view to their inclusion in the study; b) patients already hospitalised with schizophrenia; c) patients admitted to a psychiatric emergency unit.

The non-inclusion criteria were: agitated state due to some form of intoxication, use of psychostimulants, suicide risk, exposure to benzodiazepine or an antipsychotic in the 4 hours prior to administration of the study treatment. Patients with an acute or chronic lung condition were also excluded.

Patients were randomised to three groups:
- inhaled loxapine 4.5 mg,
- inhaled loxapine 9.1 mg,
- placebo.

The first dose (dose 1) was administered on randomisation.
In cases of persistent agitation, a maximum of three doses were permitted in 24 hours (a second dose at least 2 hours after dose 1, then if necessary a third dose at least 4 hours after the second dose).
Administration of lorazepam by the intramuscular route (IM) was permitted as alternative therapy 2 hours after dose 1.

The primary endpoint was the decrease in the agitation score on the PANSS-EC scale 2 hours after administration of dose 1.

Secondary endpoints included:
- decrease in the agitation score on the PANSS-EC scale 10, 20, 30, and 45 minutes after administration of dose 1;

[3] PANSS-EC Scale (Positive and Negative Syndrome Scale Excited Component) consists of five items (excitement, hostility, tension, uncooperativeness, poor impulse control) rated from 1 (no symptoms) to 7 (extremely severe symptoms).

- percentage of patients whose symptoms were “very much improved” or “much improved” 2 hours after administration of dose 1 on the CGI-I clinical global impression scale;[4]
- percentage of responder patients, defined as patients presenting ≥ 40% decrease relative to the baseline PANSS-EC score;
- number of patients having received one or two extra doses of study treatment or alternative treatment with lorazepam IM.

The number of subjects necessary was calculated at 100 per group, based on results observed in dose-finding study 004-201[5] and a power of 99% for the 9.1 mg loxapine group and 79% for the 4.5 mg loxapine group.

7.1.2 Results

7.1.2.1 Results of Study 004-301

A total of 344 patients were randomised; 338 patients completed the study.

Characteristics of the patients

Patients had a mean age of 43 years and were mostly men (73%). The patients had been diagnosed with schizophrenia a mean of 18 years previously (standard deviation [SD]: 10 years). The median duration of the agitation episode was 4 days (minimum: < 1 day; maximum: 90 days). Almost 35% of the patients were receiving antipsychotic treatment prior to inclusion.

Primary endpoint

Decreased agitation was noted in both loxapine groups in comparison with placebo 2 hours after administration of dose 1 (see Table 1 and Fig. 1).

Table 1. Variation in the PANSS-EC agitation score 2 hours after dose 1 (ITT population)

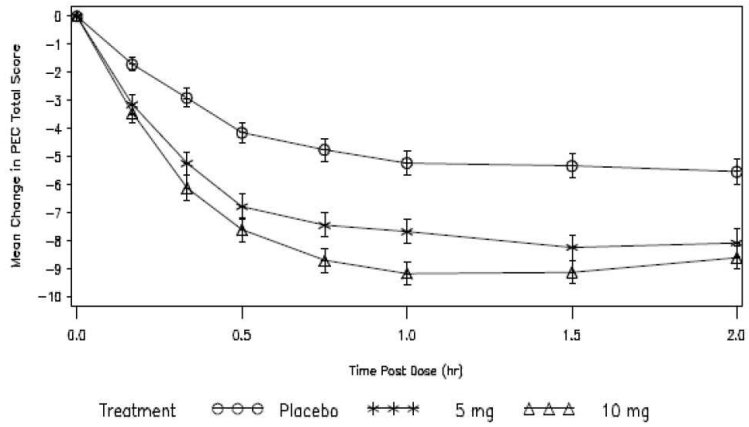
	Placebo n = 115	Loxapine 4.5 mg n = 116	Loxapine 9.1 mg n = 112
PANSS-EC on inclusion			
Mean (SD) Median (min; max)	17.4 (1.8) 17 (14; 24)	17.8 (2.3) 18 (14; 28)	17.6 (2.1) 17 (14; 27)
Change in PANSS-EC score 2 hours after Dose 1			
Mean of least squares P-value	- 5.8	- 8.0 p < 0.001	- 8.7 p < 0.0001

[4] The CGI-I Scale (Clinical Global Impression of Improvement) with externally evaluated scores of between 1 (very much improved) and 7 (very much worse).

[5] In dose-finding study 004-201 in patients presenting agitation episodes in schizophrenia, the decrease in agitation 2 hours after administration was -5.0 (SD: 4.1) in the placebo group, -6.7 (SD: 5.1) in the loxapine 5 mg group, and -8.6 (SD: 4.9) in the loxapine 10 mg group.

Secondary endpoints

A decrease in agitation in comparison with placebo was noted 10 minutes after dose 1 and then at every subsequent evaluation (cf. Fig. 1).
The percentage of patients whose symptoms were “very much improved” or “much improved” on the CGI-I scale two hours after dose 1 was 36% in the placebo group versus 57% (p = 0.015) in the loxapine 4,5 mg group, and 67% (p < 0.0001) in the loxapine 9.1 mg group.
The percentage of responder patients on the PANSS-EC scale 2 hours after dose 1 was 38% in the placebo group versus 63% (p < 0.001) in the loxapine 4.5 mg group and 70% (p < 0.0001) in the loxapine 9.1 mg group.
The proportion of patients who received an extra treatment dose or alternative treatment with lorazepam IM in the 4 hours after the first dose was 44.3% in the placebo group, 31.6% in the loxapine 4.5 mg group, and 25.0% in the loxapine 9.1 mg group.



Mean (SEM)	10 minutes	20 minutes	30 minutes	45 minutes	1 hour	1.5 hours	2 hours
Placebo:	-1.7 (0.23)	-2.9 (0.33)	-4.1 (0.38)	-4.8 (0.41)	-5.2 (0.45)	-5.3 (0.43)	-5.5 (0.46)
5 mg:	-3.1 (0.36)	-5.2 (0.42)	-6.8 (0.44)	-7.4 (0.44)	-7.7 (0.44)	-8.2 (0.45)	-8.1 (0.48)
10 mg:	-3.4 (0.34)	-6.1 (0.45)	-7.6 (0.45)	-8.7 (0.42)	-9.2 (0.42)	-9.1 (0.4)	-8.6 (0.41)

SEM=standard error of the mean

Figure 1. Variation in the PANSS-EC agitation score in the 2 hours after administration of dose 1.

7.1.2.2 Results of Study 004-302

A total of 314 patients were randomised; 312 patients completed the study.

Characteristics of the patients

Patients had a mean age of 41 years and 50% of them were men. Patients had been diagnosed with bipolar disorder a mean of 18 years previously (SD: 10 years). The median duration of the agitation episode was between 5 and 6 days (minimum: < 1 day; maximum: 210 days). Almost 13% of the patients were receiving antipsychotic treatment prior to inclusion.

Primary endpoint

Decreased agitation was noted in both loxapine groups in comparison with placebo 2 hours after the intake (cf. Table 2).

Table 2. Variation in the PANSS-EC agitation score 2 hours after dose 1 (ITT population).

	Placebo n = 105	Loxapine 4.5 mg n = 104	Loxapine 9.1 mg n = 105
PANSS-EC on inclusion			
Mean (SD) Median (min; max)	17.7 (2.8) 17 (14; 31)	17.4 (2.2) 17 (14; 26)	17.3 (2.2) 17 (14; 25)
Change in the PANSS-EC score 2 hours after intake			
Mean of least squares P-value	- 4.7	- 8.2 p < 0.0001	- 9.2 p < 0.0001

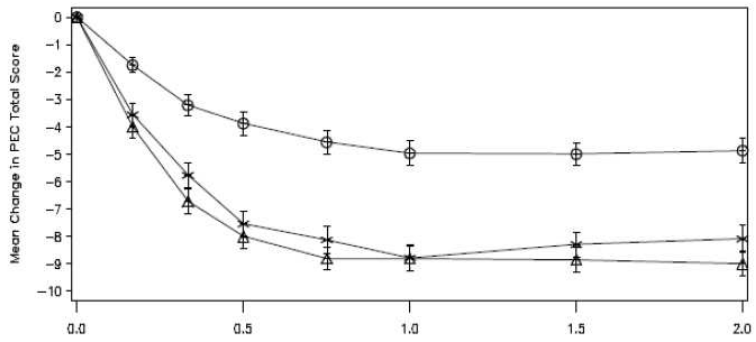
Secondary endpoints

A decrease in agitation in comparison with placebo was noted 10 minutes after dose 1 and then at every subsequent evaluation (cf. Fig. 1).

The percentage of patients whose symptoms were “very much improved” or “much improved” on the CGI-I scale 2 hours after dose 1 was 28% in the placebo group versus 66% (p < 0.0001) in the loxapine 4,5 mg group, and 74% (p < 0.0001) in the loxapine 9.1 mg group.

The percentage of responder patients on the PANSS-EC scale 2 hours after dose 1 was 28% in the placebo group versus 62% (p < 0.0001) in the loxapine 4,5 mg group, and 73% (p < 0.0001) in the loxapine 9.1 mg group.

The proportion of patients who received an extra treatment dose or alternative treatment with lorazepam IM in the 4 hours after the first dose was 63.8% in the placebo group, 40.4% in the loxapine 4.5 mg group, and 24.0% in the loxapine 9.1 mg group.



Mean (SEM)	10 minutes	20 minutes	30 minutes	45 minutes	1 hour	1.5 hours	2 hours
Placebo:	-1.8 (0.29)	-3.2 (0.39)	-3.9 (0.43)	-4.6 (0.43)	-5.0 (0.45)	-5.0 (0.42)	-4.9 (0.47)
5 mg:	-3.6 (0.4)	-5.8 (0.46)	-7.5 (0.47)	-8.1 (0.47)	-8.8 (0.46)	-8.3 (0.46)	-8.1 (0.48)
10 mg:	-4.0 (0.4)	-6.7 (0.45)	-8.0 (0.46)	-8.8 (0.43)	-8.8 (0.44)	-8.8 (0.46)	-9.0 (0.46)

Source: m5.3.5.1, CSR 004-302, Section 11.1, Tables 2.1, 2.7, 2.15

Figure 2. Variation in the PANSS-EC agitation score in the 2 hours after administration of dose 1.

07.2 Adverse effects

7.2.1 Data from clinical studies

The evaluation of the safety profile is based on three placebo-controlled clinical studies (Studies 004-301 and 302 and a dose-finding study); these studies included 524 adult patients treated with inhaled loxapine in a dose of 4.5 mg (265 patients) or 9.1 mg (259 patients).
The incidence of adverse events was comparable between the loxapine and placebo groups (35% and 39% in the loxapine groups versus 37% in the placebo group).
The adverse effects most commonly reported during treatment with inhaled loxapine were dysgeusia (13% versus 5% in the placebo group) and sedation/drowsiness (12% versus 9% in the placebo group; cf, Table 3).

Tableau 3. Adverse effects reported in at least 5% of patients treated with ADASUVE

Adverse effect n (%)	Placebo n = 263	Loxapine 4.5 mg n = 152	Loxapine 9.1 mg n = 269	Loxapine 15-30 mg n = 103
Dizziness	23 (9)	12 (8)	14 (5)	10 (10)
Sedation	20 (8)	23 (15)	25 (9)	7 (7)
Dysgeusia	13 (5)	11 (7)	37 (14)	19 (18)

Bronchospasm

In order to evaluate pulmonary tolerance to inhaled loxapine, two placebo-controlled studies were conducted in healthy volunteers with persistent mild to moderate asthma (study 004-105, 52 patients) or COPD (study 004-108, 53 patients). In both studies, two doses of loxapine were administered with an interval of 10 hours.
Bronchospasm (including wheezing, shortness of breath, or cough) were reported in 14/26 patients (54%) suffering from asthma treated with loxapine and in 5/26 patients (19%) suffering from COPD treated with loxapine. These events occurred within 25 minutes of taking loxapine in 12/14 asthma patients and 4/5 COPD patients. These events were classed as mild to moderate. Treatment with an inhaled bronchodilator was necessary in 13 asthma patients and in 2 COPD patients.

7.2.2 Risk management plan

Within the framework of the risk management plan validated with the European Medicines Agency, the major risks identified are the following: bronchospasm, extrapyramidal symptoms, and hypotension.
The major potential risks are as follows: suicide risk, QT prolongation, tardive dyskinesia, neuroleptic malignant syndrome, epilepsy, drug interactions.

07.3 Summary and discussion

◗ Two studies compared the efficacy and safety of ADASUVE in doses of 4.5 mg and 9.1 mg with that of placebo in patients with agitation episodes in association with schizophrenia (study 004-301, 344 patients) or manic episodes in bipolar disorder (study 004-302, 314 patients).
In both studies, a decrease in agitation was observed in both ADASUVE groups in comparison with placebo 2 hours after administration of an initial treatment dose:

- In patients suffering from schizophrenia (study 004-301), the decrease in the agitation score on the PANSS-EC scale was -5.8 in the placebo group versus -8 in the loxapine 4.5 mg group ($p < 0.001$) and -8.7 in the loxapine 9.1 mg group ($p < 0.0001$);
- In patients suffering from manic episodes in bipolar disorder (study 004-302), the decrease in the agitation score was -4.7 in the placebo group versus -8.2 in the loxapine 4.5 mg group ($p < 0.0001$) and -9.2 in the loxapine 9.1 mg group ($p < 0.0001$);

A decrease in agitation was noted in both groups from 10 minutes after administration of the first dose.

◗ The adverse effects most commonly reported were dysgeusia (13% versus 5% in the placebo group) and sedation/drowsiness (12% versus 9% in the placebo group). ADASUVE is contraindicated in patients with asthma or chronic obstructive pulmonary disease or presenting acute respiratory signs or symptoms.

08 THERAPEUTIC USE[1,2]

Medicinal treatment for states of agitation is an acute treatment whose aims are as follows:
- rapidly control the agitation symptoms in order to protect the patients themselves,
- prevent escalation of the situation and patients developing auto- and hetero-aggressive behaviour,
- avoid having to have recourse to physical restraint,
- ensure the resumption of dialogue, which is vital for establishing the anamnesis and clinical picture with a view to being able to determine the most appropriate clinical approach.

The medicines used are antipsychotics and/or benzodiazepines for oral or parenteral administration. The oral route is always to be preferred.

Inhaled ADASUVE is an alternative to the oral or parenteral antipsychotics and benzodiazepines used in the hospital setting for the rapid control of agitation of psychiatric origin (episodes of schizophrenia, manic episodes in bipolar disorder).

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

09.1 Actual Benefit

◗ Agitation is a psychomotor behavioural issue characterised by motor hyperactivity associated with loss of control over actions, speech, and thought. It arouses an intolerant response among family members and those around them.

◗ Inhaled ADASUVE 9.1 mg is a symptomatic treatment for the rapid control of mild to moderate agitation in adult patients with schizophrenia or bipolar disorder.

◗ The efficacy of a puff of ADASUVE versus placebo in reducing agitation has been demonstrated in two randomised double-blind studies. In both these studies, the principal adverse events were dysgeusis and sedation/drowsiness. ADASUVE is contraindicated in patients with asthma or COPD.

◗ The treatment alternatives are the oral or parenteral antipsychotics and benzodiazepines generally used in the management of agitation states of psychiatric origin.

◗ The proprietary medicinal product ADASUVE is not expected to have any impact on public health.

Taking account of these points, the Committee considers that the actual benefit of ADASUVE is substantial.

09.2 Improvement in Actual Benefit

ADASUVE does not provide any improvement in actual benefit (level V, non-existent) in the rapid control of mild to moderate agitation in adult patients with schizophrenia or bipolar disorder.

09.3 Target population

The target population for ADASUVE is difficult to quantify.
According to a 2003 survey, hospital accident and emergency departments receive, on average, 2000 patients a month. The estimated prevalence of agitation states is said to be 1.22% of patients admitted.[6] Agitation states of psychiatric origin would appear to account for 62% of cases.[1]

[6] Bourdinaud et al. Enquête sur la prise en charge des états d'agitation dans les services d'accueil et d'urgences en France. L'encéphale 2003; 24: 89-98.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the rapid control of mild to moderate agitation in adult patients with schizophrenia or bipolar disorder.

◗ Packaging

It is appropriate for the prescribing conditions according to the indication, the dose, and the treatment duration.