HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 November 2011

SYCREST 5 mg, sublingual tablet
B/60 (CIP code: 415 241-6)
B/100 (CIP code: 579 353-1)

SYCREST 10 mg, sublingual tablet
B/60 (CIP code: 415 242-2)
B/100 (CIP code: 579 354-8)

Applicant: LUNDBECK SAS

Asenapine
ATC code: N05AH05 (antipsychotics)

List I

Date of Marketing Authorisation (centralised procedure): 01/09/2010

Reason for the request: Inclusion on list of products refundable by National Health Insurance and for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Asenapine

1.2. Indication

“SYCREST is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.”

SYCREST has been refused Marketing Authorisation in Europe in the treatment of schizophrenia.[1]

1.3. Dosage (see SPC)

“The recommended starting dosage of SYCREST as monotherapy is 10 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be reduced to 5 mg twice daily according to clinical assessment. For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily.”

[1] European public assessment report for SYCREST. EMA/CHP/583011/2010.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

N	Nervous system
N05	Psycholeptics
N05A	Antipsychotics
N05AH	Diazepines, oxazepines and thiazepines
N05AH05	Asenapine

2.2. Medicines in the same therapeutic category

- Oral antipsychotics having an indication in the treatment of moderate to severe manic episodes of bipolar disorder

INN (proprietary medicinal products)	**MA indications in the treatment of bipolar disorder**	**AB**
Aripiprazole (ABILIFY)	▪ Treatment of moderate to severe manic episodes of bipolar I disorder ▪ Preventing relapse of manic episodes in patients who have presented predominantly manic episodes and in whom the manic episodes have responded to treatment with aripiprazole.	Substantial
Olanzapine (ZYPREXA, ZYPREXA VELOTAB)	▪ Treatment of moderate to severe manic episodes. ▪ Prevention of relapses in patients presenting bipolar disorder who have already responded to olanzapine treatment during a manic episode.	Substantial
Quetiapine (SEROQUEL XR)	▪ Treatment of moderate to severe manic episodes in bipolar disorder. ▪ Treatment of major depressive episodes in bipolar disorder. ▪ Prevention of relapses in patients presenting bipolar disorder who have already responded to quetiapine treatment during a manic or depressive episode.	Substantial (manic episodes and depressive episodes) Insufficient (prevention of relapses)
Risperidone (RISPERDAL and generics, RISPERDALORO)	▪ Treatment of moderate to severe manic episodes in bipolar disorder.	Substantial

2.3. Medicines with a similar therapeutic aim

- Mood stabilisers having an indication in the treatment of moderate to severe manic episodes of bipolar disorder

INN (proprietary medicinal products)	**MA indications in the treatment of bipolar disorder**	**AB**
Lithium (TERALITHE, TERALITHE LP)	▪ Prevention of relapses of bipolar disorder and intermittent schizoaffective states. ▪ Curative treatment of manic or hypomanic states of excitement.	Substantial
Carbamazepine (TEGRETOL, TEGRETOL LP and generics)	▪ Prevention of relapses in bipolar disorder, especially in patients presenting relative resistance, contra-indications or an intolerance to lithium. ▪ Treatment of manic or hypomanic states of excitement.	Substantial
Sodium valproate (DEPAKOTE)	▪ Treatment of manic episodes in patients suffering from bipolar disorder in cases of contraindication or intolerance to lithium. Continuation of the treatment during the course of the manic episode may be considered in patients who have responded to the acute treatment of this episode.	Substantial

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy data in the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults

3.1.1. Asenapine as monotherapy

Demonstrating the efficacy of asenapine as monotherapy in the treatment of moderate to severe manic episodes in bipolar I disorder relies on two three-week studies (ARES 3A and ARES 3B) with a nine-week extension phase for each of them (study ARES 9).

3.1.1.1. ARES 3A and ARES 3B studies

The aim of the ARES 3A and ARES 3B studies was to demonstrate the superiority of asenapine over placebo at three weeks in adult subjects presenting manic or mixed phase type I bipolar disorder.

a) Methods

Both studies, ARES 3A and ARES 3B, use the same methods.
These are two three-week randomised, double-blind, placebo-controlled studies with an active control (olanzapine).

Patients included were adults presenting a manic or mixed episode of bipolar I disorder (DSM-IV) that had started less than three months previously with a score on the YMRS[2] scale ≥ 20. Rapid-cycling patients were excluded from these studies.

Patients were randomised into three parallel groups (2:2:1) to receive:
- asenapine: 5 mg × 2 on D1 then 5 to 10 mg twice daily;
- olanzapine: 15 mg on D1 then 5 to 20 mg/day;
- or a placebo.

The primary efficacy endpoint was the variation in the score on the YMRS scale[1] after three weeks of treatment with respect to the baseline value.

The principal secondary endpoints were:
- the percentage of responder patients (50% decrease in the YMRS score on D21 with respect to the baseline value)
- percentage of patients in remission (total score on the YMRS scale ≤ 12 on D21)
- the variation with respect to inclusion in the severity of the mania (CGI-BP[3] scale).

A statistical comparison of asenapine and olanzapine in terms of efficacy or tolerability was not allowed for in the protocol.

b) Results of the ARES 3A study

In all, 488 patients were randomised and treated in one of the treatment arms: 98 in the placebo arm, 185 in the asenapine arm and 205 in the olanzapine arm.
The patients had a diagnosis of manic (69%) or mixed (31%) episodes. The average age was 39 years and 53% of them were men.
During the study, the average dose of asenapine was 18.4 mg/day and the average dose of olanzapine 15.9 mg/day.

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[2] The YMRS (Young Mania Rating Scale) allows the severity of a manic episode to be assessed (score > 20) in patients with bipolar disorder. The score goes from 0 to 60.

[3] The CGI-BP (Clinical Global Impression) scale enables the investigator to estimate the severity of the bipolar symptoms going from the “not at all ill” score to the “extremely severe” score (7 points).

Fifty-seven patients (58.2%) in the placebo group, 124 patients (67.0%) in the asenapine group and 161 patients (78.5%) in the olanzapine group completed the study.
The reasons for dropping out are given in Table 1.

Table 1. Drop-out numbers and reasons

	Placebo n ITT = 94	Asenapine n ITT = 183	Olanzapine n ITT = 203
Drop-outs, n (%)	**41 (41,8)**	**61 (33,0)**	**44 (21,5)**
Reason for dropping out, n (%)			
Adverse event	**4 (4.1)**	17 (9.2)	7 (3.4)
Lack of efficacy	**14 (14.3)**	14 (7.6)	13 (6.3)
Consent withdrawn	**13 (13.3)**	25 (13.5)	15 (7.3)
Lost from sight	**4 (4.1)**	1 (0.5)	6 (2.9)
Other	**6 (6.1)**	4 (2.2)	3 (1.5)

ITT: intention to treat

Primary efficacy endpoint:
At three weeks, the improvement in the total YMRS score in the asenapine group was higher than that in the placebo group: the mean variation in the YMRS score was -11.5 ± 0.8 in the asenapine group and -7.8 ± 1.1 in the placebo group (p = 0.0065; ITT-LOCF population).
The mean variation in the YMRS scores is detailed in Table 2.

Table 2. YMRS score on inclusion and after three weeks of treatment (ITT-LOCF population[4])

	Initial YMRS score Mean ± SD	**YMRS score on D21** Mean ± SD	**Score variation on D21** Mean of LS† ± SE	**p***
Placebo, n = 94	28.3 ± 6.3	20.4 ± 12.7	-7.8 ± 1.1	
Asenapine, n = 183	29.4 ± 6.7	17.7 ± 11.9	-11.5 ± 0.8	0.0065
Olanzapine, n = 203	29.7 ± 6.7	14.9 ± 10.5	-14.6 ± 0.8	< 0.0001

SD: standard deviation; mean of LS: mean of least squares; SE: standard error; † according to an ANCOVA model; * versus placebo, according to an ANCOVA model

Secondary endpoints:
- the proportion of responder patients was 42.6% in the asenapine group and 34.0% in the placebo group (difference not significant, p = 0.1951);
- the proportion of patients in remission was 35.5% in the asenapine group and 30.9% in the placebo group (difference not significant, p = 0.5033);
- the improvement in the mean severity scores on the CGI-BP scale was greater in the asenapine group than in the placebo group: -1.2 ± 0.1 versus -0.8 ± 0.13 (p = 0.0116).

Olanzapine was more effective than placebo at three weeks, including on the proportions of responder patients and patients in remission, in contrast to asenapine:
- the mean variation in the YMRS score was -14.6 ± 0.8 (p < 0.0001);
- the proportion of responders was 54.7% (p = 0.0011);
- the proportion of patients in remission was 46.3% (p = 0.0159).

c) Results of the ARES 3B study

In all, 488 patients were randomised and treated in one of the treatment arms: 104 in the placebo arm, 194 in the asenapine arm and 190 in the olanzapine arm.
The patients had a diagnosis of manic (69%) or mixed (31%) episodes. The average age was 39 years with 57% of men.
During the study, the average dose of asenapine was 18.2 mg/day and of olanzapine 15.8 mg/day.

Sixty-four patients in the placebo group (61.5%, 122 patients in the asenapine group (62.9%) and 152 patients in the olanzapine (79.6%) completed the study.

[4] Last observation carried forward

The reasons for dropping out are given in Table 3.

Table 3. Drop-out numbers and reasons

	Placebo n ITT = 103	Asenapine n ITT = 189	Olanzapine n ITT = 188
Drop-outs, n (%)	40 (38.5)	72 (37.1)	39 (20.4)
Reason for dropping out, n (%)			
Adverse event	**7 (6.7)**	20 (10.3)	8 (4.2)
Loss of efficacy	**17 (16.3)**	16 (8.2)	11 (5.8)
Consent withdrawn	**13 (12.5)**	28 (14.4)	16 (8.4)
Lost from sight	**2 (1.9)**	5 (2.6)	2 (1.0)
Other	**1 (1.0)**	3 (1.5)	2 (1.0)

Primary efficacy endpoint:
At three weeks, the improvement in the total YMRS score in the asenapine group was higher than that in the placebo group: the mean variation in the YMRS score was -10.8 ± 0.8 in the asenapine group and -5.5 ± 1.0 in the placebo group ($p < 0.0001$; ITT-LOCF population).
The mean variation in the YMRS scores is detailed in Table 4.

Table 4. YMRS score on inclusion and after three weeks of treatment (ITT-LOCF population)

	Initial YMRS score Mean ± SD	**YMRS score on D21** Mean ± SD	**Score variation on D21** Mean of LS† ± SD	**p***
Placebo, n = 103	29.0 ± 6.1	23.5 ± 12.6	- 5.5 ± 1.0	
Asenapine, n = 189	28.3 ± 5.5	17.7 ± 11.3	- 10.8 ± 0.8*	< 0.0001
Olanzapine, n = 188	28.6 ± 5.9	16.1 ± 9.4	-12.6 ± 0.8	< 0.0001

SD: standard deviation; mean of LS: mean of least squares; SE: standard error; † according to an ANCOVA model; * versus placebo, according to an ANCOVA model

Secondary endpoints:
- the proportion of responder patients in the asenapine group was greater than the proportion of responder patients in the placebo group: 42.3% versus 25.2% ($p = 0.0049$).
- the proportion of patients in remission in the asenapine group was greater than the proportion of patients in remission in the placebo group: 40.2% versus 22.3% ($p = 0.0020$).
- the improvement in the mean severity scores on the CGI-BP scale was greater in the asenapine group than in the placebo group: -1.2 ± 0.1 versus -0.7 ± 0.1 ($p = 0.0017$).

Olanzapine was more effective than placebo at three weeks:
- the mean variation in the YMRS score was -12.6 ± 0.8 ($p < 0.0001$);
- the proportion of responder patients was 50.0% ($p < 0.0001$);
- the proportion of patients in remission was 39.4% ($p = 0.0041$).

3.1.1.2. Nine-week extension study: ARES 9

The ARES 9 study is an extension of the ARES 3A and ARES 3B studies.
The aim was to demonstrate the non-inferiority of asenapine in comparison to olanzapine as regards maintaining treatment efficacy at twelve weeks in patients who had completed either of the studies ARES 3A or 3B.

a) Methods

This study included patients who had completed the three-week ARES 3A and ARES 3B studies without lifting the double-blinding and without fresh randomisation.
The patients continued with their treatment with asenapine (5 at 10 mg twice daily) or olanzapine (5 to 20 mg/day).
Participants who had received placebo during the three-week studies were treated with asenapine (5 to 10 mg twice daily) and were included for the tolerance analyses only.

The principal criterion was the variation in the score on the YMRS scale after twelve weeks of treatment with respect to the baseline value on inclusion in the ARES 3A and 3B studies.

b) Results

Seventy-six patients (22%) who had completed the ARES 3A study and 100 patients (30%) who had completed the ARES 3B study were not included in the ARES 9 extension phase, principally on the grounds of withdrawal of consent (83% of the reasons for non-inclusion for the ARES 3A study and 76% for the ARES 3B study).
In all, 504 patients were included in ARES 9 extension phase: 94 who had previously received placebo, 181 who had received asenapine and 229 who had received olanzapine.
The average dose of asenapine was 17.6 mg/day and of olanzapine 16.1 mg/day.

One hundred and twelve patients (61.9%) in the asenapine group and 146 patients (63.8%) in the olanzapine group completed the study.

Primary efficacy endpoint:
At 12 weeks, the mean variation in the YMRS score was -24.4 ± 8.7 in the asenapine group and -23.9 ± 7.9 in the olanzapine group ($p < 0.0001$).
The mean variation in the YMRS scores is detailed in Table 5.

Table 5. Efficacy result versus olanzapine at 12 weeks of treatment (per protocol population)

	Initial YMRS score Mean ± SD	**YMRS score on D84** Mean ± SD	**Score variation on D84** Mean ± SE	**Score variation on D84** Mean of LS† ± SE	**p†**
Asenapine, n = 86	29.6 ± 6.1	5.2 ± 6.0	- 24.4 ± 8.7	- 27.3 ± 0.6	< 0.0001
Olanzapine, n = 128	28.8 ± 5.4	4.9 ± 5.3	- 23.9 ± 7.9	- 23.7 ± 0.5	

SD: standard deviation; mean of LS: mean of least squares; SE: standard error; † according to an ANCOVA model

The proportion of responder patients (50% decrease in the YMRS score) at twelve weeks was 89.5% in the asenapine group and 92.2% in the olanzapine group.
The proportion of patients in remission (total score on the YMRS scale ≤ 12) at twelve weeks was 88.4% in the asenapine group and 90.6% in the olanzapine group.

3.1.2. Asenapine in combination with a mood stabiliser

In support of its application the company submitted a study versus placebo assessing the efficacy and tolerance at twelve weeks of adjunctive therapy with asenapine in patients partially non-responsive to lithium or valproate monotherapy for two weeks.

3.1.2.1. Apollo 12 study

The aim of the study was to demonstrate the superiority of asenapine over placebo at three weeks in adult patients presenting manic or mixed phase bipolar I disorder for less than three months on inclusion and non-responders to lithium or valproate.

a) Methods

The Apollo 12 study is a 12-week, randomised, double-blind, placebo-controlled study.

Patients included were adults presenting a manic or mixed bipolar I disorder (DSM-IV) that had started less than three months previously with a score ≥ 20 on the YMRS mania scale on inclusion and treated for at least the previous two weeks with lithium or valproate. On inclusion, the serum lithium concentration had to be between 0.6 and 1.2 mmol/l and the serum valproate concentration between 50 and 125 µg/ml.

The patients were randomised into two groups to receive in combination with the mood stabiliser (lithium or valproate continued in open mode):
- asenapine: 5 mg × 2 on D1 then 5 to 10 mg twice daily;
- or a placebo.

The primary efficacy endpoint was the variation in the score on the YMRS scale after three weeks of treatment with respect to the baseline value.

The principal secondary endpoints were:
- the percentage of responder patients (50% decrease in the YMRS score with respect to the baseline value);
- percentage of patients in remission (total score on the YMRS scale ≤ 12);
- the variation with respect to inclusion in the severity of the mania (CGI-BP scale).

b) Results

In all, 326 patients were randomised into one of the three treatment arms: 159 in the asenapine/mood stabiliser group and 167 in the placebo/mood stabiliser group.
The average age was 39 years and 58% were men. The patients had a diagnosis of manic (61%) or mixed (39%) episodes.
The average dose of asenapine was 11.8 mg/day.

Sixty-one patients (38.4%) in the asenapine/mood stabiliser group and 55 patients (32.9%) in the placebo/mood stabiliser group continued the study for the full 12 weeks envisaged in the protocol.
The reasons for dropping out are detailed in Table 6.

Table 6. Drop-out numbers and reasons

	Placebo/mood stabiliser n ITT = 163	**Asenapine/mood stabiliser** n ITT = 155
Drop-outs, n (%)	**112 (67.1)**	**98 (61.6)**
Reason for dropping out, n (%)		
Adverse event	**19 (11.4)**	25 (15.7)
Loss of efficacy	**27 (16.2))**	13 (8.2)
Consent withdrawn	**36 (21.6)**	34 (21.4)
Lost from sight	**21 (12.6)**	17 (10.7)
Other	**9 (5.4)**	9 (5.7)

Primary efficacy endpoint:
At three weeks, the improvement in the total YMRS score was greater in the asenapine/mood stabiliser group than in the placebo/mood stabiliser group: the mean variation in the score was -10.3 ± 0.8 in the asenapine/mood stabiliser group and -7.9 ± 0.8 in the placebo/mood stabiliser group (p = 0.0257; ITT-LOCF population).
The mean variation in the YMRS scores is detailed in Table 7.

Table 7: Mean variation in the YMRS score after three weeks of treatment (ITT-LOCF population)

	Initial YMRS score Mean ± SD	**YMRS score on D21** Mean ± SD	**Score variation on D21** Mean ± SE	**Score variation on D21** Mean of LS† ± SE	**p†**
Placebo/mood stabiliser n ITT = 163	28.2 ± 5.8	20.5 ± 10.4	- 7.7 ± 9.6	- 7.9 ± 0.8	0.0257
Asenapine/mood stabiliser n ITT = 155	28.0 ± 5.6	18.2 ± 10.3	- 9.7 ± 10.1	- 10.3 ± 0.8	

SD: standard deviation; mean of LS: mean of least squares; SE: standard error; † according to an ANCOVA model

The complementary OC[5] and mixed model analyses for repeated measurements (MMRM) did not show any difference between the two treatment groups.

Primary efficacy endpoints:
After three weeks,
- the percentage of responder patients was 34.2% in the asenapine/mood stabiliser group and 27.0% in the placebo/mood stabiliser group (p = 0.1634);
- the percentage of patients in remission was higher in the asenapine/mood stabiliser group than in the placebo/mood stabiliser group: 33.5% versus 21.5% (p = 0.0158).

After 12 weeks,
- the improvement in the total YMRS score was greater in the asenapine/mood stabiliser group than in the placebo/mood stabiliser group: the mean variation in the score was -12.7 ± 0.9 in the asenapine/mood stabiliser group versus -9.3 ± 0.9 in the placebo/mood stabiliser group (p = 0.0073).
- the percentage of responder patients was higher in the asenapine/mood stabiliser group than in the placebo/mood stabiliser group: 47.7% versus 34.4% (p = 0.0152);
- the percentage of patients in remission was higher in the asenapine/mood stabiliser group than in the placebo/mood stabiliser group: 43.2% versus 30.1% (p = 0.0148).

3.1.3. Meta-analysis by Yildiz et al., 2010[6]

Yildiz et al published a meta-analysis seeking to compare the efficacy of the different treatments used as monotherapy in the management of manic episodes in bipolar disorder.
The meta-analysis included 38 clinical studies assessing the efficacy of 17 products versus placebo. The ARES 3A and ARES 3B studies assessing asenapine as monotherapy at three weeks have been included in the meta-analysis.
In all, 13 products were found to be more effective than the placebo. Among them, 7 products are available in France with an indication in the treatment of manic episodes in bipolar disorder: aripiprazole, asenapine, lithium, olanzapine, quetiapine, risperidone and valproate. The grouped effect size of the 13 products (Hedges's g) was 0.42 [0.36-0.48], corresponding to a moderate size of effect.
Antipsychotics as a group (second-generation antipsychotics or haloperidol) have exhibited a greater effect size than mood stabilisers (Hedges's g = 0.18 [0.08-0.28]).
The effect size of asenapine versus placebo (Hedges's g = 0.40 [0.13-0.66]) was equivalent to the mean size effect of atypical antipsychotics (Hedges's g = 0.40 [0.32-0.47].

[5] Observed case
[6] Yildiz et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. Neuropsychopharmacology. 2010 (1-15)

3.2. Adverse effects

3.2.1. Number of patients exposed to asenapine within the framework of phase II and III clinical studies

In all, 3457 patients were exposed to asenapine in the course of the phase II and III studies into the treatment of schizophrenia (2826 patients) and in the treatment of manic episodes in bipolar disorder (631 patients). A list of the study populations is presented in Table 8 and the duration of exposure of patients to asenapine in Table 9.

Table 8. Number of patients included in the phase II and III studies

	PBO	Asenapine					
		<5 mg BID	5 mg[a] BID	10 mg[a] BID	5-10 mg[b] BID	5-10 mg BID total[c]	**All**
Schizophrenia trials	695	298	274	208	2046	2528	2826
Bipolar mania trials	369	0	0	0	631	631	631
TOTAL	1064	298	274	208	2677	3159	3457

Table 9. Duration of exposure to asenapine

	Schizophrenia trials (N=2826)	Bipolar mania trials (N=631)
	n (%)	n (%)
1 day or less	32 (1.1)	18 (2.9)
2 days to ≤1 week	156 (5.5)	81 (12.8)
>1 week to ≤4 weeks	506 (17.9)	214 (33.9)
>4 to ≤12 weeks	618 (21.9)	148 (23.5)
>12 to ≤26 weeks	431 (15.3)	50 (7.9)
>26 to ≤52 weeks	629 (22.3)	79 (12.5)
More than 52 weeks	454 (16.1)	41 (6.5)

3.2.2. Adverse events

In all the phase II and III studies taken together (3457 patients in the indications schizophrenia and bipolar disorder), the most common adverse events regarded as associated with asenapine (incidence ≥ 2% and at least double that observed with placebo) were:

- Sedation (9.1% asenapine, 4.4% placebo),
- Somnolence (8.4% asenapine, 2.3% placebo),
- Akathisia (5.4% asenapine, 2.4% placebo),
- Oral hypoaesthesia* (5.0% asenapine, 0.7% placebo),
- Weight gain (3.5% asenapine, 0.4% placebo).

* Asenapine has anaesthetic properties. Oral hypoaesthesia and paraesthesia may appear immediately after administration and usually wear off in 1 hour.

Point on neurological tolerance, weight gain, and metabolic and cardiovascular effects of asenapine:

- extrapyramidal symptoms (EPS):

In the three-week studies into bipolar disorder, the incidence of extrapyramidal symptoms was 10% in the asenapine group versus 4.4% for the placebo and 9.4% for olanzapine.
In all the phase II and III studies taken together (schizophrenia and bipolar disorder), 14 cases of tardive dyskinesia were reported in the subjects treated with asenapine, i.e. an incidence of 0.4% (incidence 1.0 per 100 patient-years). Two cases occurred in the placebo group (0.2%, an incidence of 1.4 per 100 patient-years), one in the haloperidol group (0.9%, incidence of 2.9 per 100 patient-years) and none in the risperidone or olanzapine groups.

- weight gain:

In the three-week studies into bipolar disorder, the mean weight gain was 1.3 kg in the asenapine group 5 to 10 mg twice daily, 0.2 kg in the placebo group and 2.3 kg in the olanzapine group.
In all the phase II and III studies taken together (schizophrenia and bipolar disorder), the mean weight gain was 0.8 kg for asenapine versus 3.5 kg for olanzapine. The incidence of weight gain ≥ 7% was 31.7% (n = 344) for olanzapine, 12.6% for asenapine (n = 374), 14.6% for risperidone (n = 13) and 8.4% for haloperidol (n = 9).

- metabolic effects:

In all the phase II and III studies taken together (schizophrenia and bipolar disorder), the mean increase in cholesterolaemia was 0.4% under asenapine and 1.1% under olanzapine. The mean increase in triglyceridaemia was 0.8% under asenapine and 1.7% under olanzapine. A smaller proportion of patients in the asenapine group moved into the higher category of cholesterolaemia (15.6% asenapine versus 24.3% with olanzapine) or triglyceridaemia (26.1% asenapine versus 40.7% with olanzapine).
The incidence of adverse effects like hyperglycaemia and diabetes was small and comparable between asenapine and olanzapine (1.0% versus 1.1%).
The proportion of patients presenting a glycated haemoglobin level ≥ 7.0% was 5.3% for olanzapine and 3.8% for asenapine. For subjects presenting a non-pathological glycated haemoglobin level on inclusion (< 6.5%), the proportion of patients presenting a level ≥ 7.0% at the end of the studies was 2.1% under olanzapine and 1.5% under asenapine.

- cardiovascular effects:

In the phase II and III studies (schizophrenia and bipolar disorder), the incidence of adverse events linked to the extension of the QT interval was comparable under asenapine to that observed under olanzapine (0.8% versus 0.7%).
The incidence of orthostatic hypotension and syncope was comparable in the asenapine and olanzapine groups (0.4%).
Elderly patients are especially at risk from presenting orthostatic hypotension.
As with other antipsychotics, the following have also been associated with taking asenapine: elevated prolactin levels, cases of neutropenia, malignant neuroleptic syndrome, accommodation disorder and transient elevation of hepatic enzymes (see SPC).
Since it came onto the market, severe hypersensitivity reactions have been reported in patients treated with asenapine, including swelling of the tongue and throat (pharyngeal oedema).

3.3. Conclusion

The efficacy of asenapine in the short-term treatment of manic episodes in bipolar disorder has been assessed in monotherapy and in combination with a mood stabiliser:

- As monotherapy:
  - asenapine (5 mg to 10 mg twice daily) showed a greater efficacy than placebo in reducing manic symptoms after three weeks of treatment in two studies including 976 patients (ARES 3A and ARES 3B studies): the mean variation in the YMRS score was -11.5 ± 0.8 in the asenapine group versus -7.8 ± 1.1 in the placebo group in the ARES 3A study and -10.8 ± 0.8 in the asenapine group versus -5.5 ± 1.0 in the placebo group in the ARES 3B study. However, the proportion of responders (50% decrease in the YMRS score on D21 with respect to the baseline value) and patients in remission (total score on the YMRS scale ≤ 12 on D21) was no different under asenapine than under placebo in the ARES 3A study.
  - asenapine (5 to 10 mg twice daily) was compared with olanzapine during 12 weeks of treatment in 504 patients who had completed previous studies (ARES 9 study): the reduction in manic symptoms measured by the mean decrease in the YMRS score was -24.4 (± 8.7) points with asenapine and -23.9 (±7.9) points with olanzapine. The non-inferiority of asenapine compared to olanzapine was not demonstrated.[7]
  - in a published meta-analysis (Yildiz et al in 2010), the effect size of asenapine as monotherapy in the short-term treatment of manic episodes was comparable to that of other antipsychotics available in this indication.

- In combination with a mood stabiliser (lithium or valproate):
  - asenapine was more effective than placebo in reducing manic symptoms at three weeks in a study including 326 patients (Apollo 12 study): the mean variation in the YMRS score was -10.3 in the asenapine/mood stabiliser group and -7.9 in the placebo/mood stabiliser group (p = 0.0257).

Regrettably there are no studies assessing the efficacy of asenapine in preventing recurrence in bipolar disorder.

In terms of tolerance, the adverse events most commonly reported in phase II and III clinical studies regarded as being associated with asenapine (incidence ≥ 2% and at least double that observed under placebo) were somnolence, weight gain, sedation, akathisia and oral hypoaesthesia.
Other adverse events such as malignant neuroleptic syndrome, seizures, orthostatic hypotension, hyperprolactinaemia, neutropaenia, accommodation disorder, hyperglycaemia and transient increase in hepatic enzymes have also been reported with asenapine.

The CHMP considered the dosage scheme proposed by the company (5 to 10 mg twice daily) in the treatment of manic episodes in bipolar disorder to be acceptable but called for a complementary dose-finding study specific to this indication to be carried out as part of the post-MA follow-up programme.[7]

[7] European public assessment report for SYCREST. EMA/CHP/583011/2010.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

▪ **In the management of bipolar disorder**

Bipolar disorder is characterised by a propensity to present marked and recurrent mood swings. Bipolar I disorder is essentially characterised by the onset of one or more manic episodes or mixed episodes. For the patient, bipolar disorder involves a chronic vulnerability due to the more or less constant mood swings and requires lifetime support.
Bipolar disorder can mean a marked deterioration in quality of life and result in a social handicap. The major risk incurred is suicide.

The efficacy/adverse effects ratio of SYCREST in this indication is high.

SYCREST is a symptomatic treatment for moderate to severe manic episodes in bipolar I disorder. SYCREST is not indicated in the prevention of recurrence in bipolar disorder.

Public health benefit:
The public health burden that bipolar disorder represents is substantial, given its frequency and severity.
Improved treatment of bipolar disorder is a public health need which is an established priority (French 2004 Law on Public Health[8], GTNDO[9]).
In light of the available data versus placebo and olanzapine, it is not anticipated that the proprietary medicinal product SYCREST will have any additional impact on morbidity and mortality or on quality of life in the treatment of manic episodes in comparison with existing treatments.
Therefore, the proprietary medicinal product SYCREST would not be expected to provide any additional response to an identified public health need.
Consequently, SYCREST is not expected to benefit public health in this indication.

There are treatment alternatives.

The actual benefit of SYCREST in this indication is **substantial**.

4.2. Improvement in actual benefit (IAB)

SYCREST does not offer any improvement in actual medical benefit (level V) in the management of moderate and severe acute manic episodes associated with bipolar I disorder in adults.

[8] French Law on Public Health 2004 - 806 of 9 August 2004: Targeting neuropsychiatric disorders
[9] GTNDO (National group of experts defining French public health objectives) (DGS-2003)

4.3. Therapeutic use[10,11,12,13,14]

Drug treatment for bipolar disorder during manic or mixed acute or hypomanic episodes relies primarily on lithium, valproate or an antipsychotic. In France, five second-generation antipsychotics are available in this indication: olanzapine, risperidone, aripiprazole, quetiapine and now asenapine.
Whenever possible, preference should be given to monotherapy.
Treatment strategies for refractory forms may include combination therapies involving various psychotropic agents (antipsychotic + lithium or valproate).
Along with the drug treatment it is necessary to offer the patient educational and psychological support: psychoeducation, lifestyle adjustments, support psychotherapy.
SYCREST does not have any indications in preventing relapses of bipolar disorder.

4.4. Target population

According to Pini et al,[15] most European studies estimate the prevalence of bipolar disorder at around 1% (0.5 to 1.1%).
Based on these estimates, France would have between 300,000 and 700,000 patients with bipolar disorder.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

The transparency Committee regrets the lack of any studies assessing the efficacy of asenapine in preventing recurrence in bipolar disorder.

[10] Llorca et al. Recommandations formalisées d'experts. L'Encéphale (2010) Supplément 4, S86–S102
[11] Haute Autorité de Santé. Bipolar disorder. Guide – Long-term conditions. HAS; 2009.
[12] National Institute for Health and Clinical Excellence. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Nice clinical guideline 38; June 2006.
[13] Grunze et al. The World Federation of Societies of Biological Psychiatry (WFSBP). Guidelines for the Biological Treatment of Bipolar disorder: Update 2009 on the treatment of acute mania. World J Biol Psychiatry 2009; 10: 85-116.
[14] Yatham et al. Bipolar disorders 2009: 11: 225–255
[15] Pini et al. Prevalence and burden of bipolar disorder in European countries. Eur Neuropsychopharmacol. 2005 Aug; 15 (4): 425-34.