HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
04 December 2013

SELINCRO 18 mg, film-coated tablets

B/7 (CIP: 34009 274 433 1 2)
B/14 (CIP: 34009 274 434 8 0)
B/28 (CIP: 34009 274 435 4 1)
B/42 (CIP: 34009 585 155 3 8)
B/98 (CIP: 34009 585 157 6 7)

Applicant: LUNDBECK

INN	nalmefene
ATC code (2014)	N07BB05 (drug used in alcohol dependence)
Reason for the request	**Inclusion**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17): B/7, B/14, B/28 **Hospital use** (French Public Health Code L.5123-2): B/7, B/14, B/28, B/42, B/98
Indication(s) concerned	**"SELINCRO is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification.** **SELINCRO should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.** **SELINCRO should be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment. "**

Actual Benefit	**Moderate**
Improvement in Actual Benefit	**In light of the available data, the Committee considers that SELINCRO, in conjunction with psychosocial support, provides a minor improvement in actual benefit (IAB IV) compared with psychosocial support alone in the treatment of alcohol dependence.**
Therapeutic Use	**SELINCRO, in conjunction with psychosocial support, is a treatment option in the reduction of alcohol consumption in adult patients who have alcohol dependence with a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. The potential benefit of the treatment depends on the patient's compliance.**
Recommendations	**This opinion depends on the applicant, together with leading centres for alcohol dependence, putting together an information sheet for prescribers defining the treatment methods: admission criteria, follow-up with systematic re-assessment at 6 months and discontinuation of the treatment. This sheet should be validated by the Haute Autorité de Santé [French National Authority for Health].** **<u>Conditions for prescribing and use</u>:** **Given the difficulty in transposing the results of the clinical trials to real life due, on the one hand, to the weakness in the effect size of this product and the frequent discontinuations (40%) of treatment observed in the studies, and, on the other hand, to the need for psychosocial support which GPs will not find feasible in general practice, the Committee recommends:** **- Pursuant to articles L.5123-2 of the public health code and L.162-17 of the social security code that the initial prescription of SELINCRO is restricted during the first year to addiction and alcohol specialists, the doctors from CSAPA or the doctors from hospital addiction units.** **- a real life follow-up of conditions for use of this product, and its impact on morbidity so as to proceed to a re-assessment in a year's time.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	25 February 2013 (centralised procedure)
Prescribing and dispensing conditions / special status	Medicine for medical prescription only

ATC Classification	2014	
	N	Nervous system
	N07	Other nervous system drugs
	N07B	Drugs used in addictive disorders
	N07BB	Drugs used in alcohol dependence
	N07BB05	nalmefene

02 BACKGROUND

The applicant is requesting inclusion of SELINCRO on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

SELINCRO is the first medicinal product with a European Marketing Authorisation for the "reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification, in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption."

03 THERAPEUTIC INDICATIONS

"SELINCRO is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification.

SELINCRO should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

SELINCRO should be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment. "

04 DOSAGE

"SELINCRO is to be taken as-needed: on each day the patient perceives a risk of drinking alcohol, one tablet should be taken, preferably 1 to 2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking SELINCRO, the patient should take one tablet as soon as possible.
The maximum dose of SELINCRO is one tablet per day. "

05 THERAPEUTIC NEED

Alcohol dependence is a chronic disease characterised by a loss of control in alcohol consumption and the possible but non-systematic occurrence of signs of physical or psychological tolerance of alcohol. It can cause internal damage to the digestive tract, liver and central nervous system, as well as death linked to this damage or by suicide or exclusion from social life, family and work.

Excessive, acute or chronic alcohol consumption is a common cause of premature death. The main causes of death are cirrhosis, chronic pancreatitis, upper aerodigestive tract cancers, strokes, cardiovascular disease, acute pneumopathy, accidents, violence: suicide or attacks on others.[1]

There are various ways of treating alcohol dependence. The treatment objective involves two steps.[1]
The first step is to encourage the patient to achieve complete abstinence (withdrawal). This is often done in a hospital environment.
The second step aims to *maintain this abstinence* for as long a period as possible. This is difficult and often interspersed with reappearance of excessive alcohol consumption. A good carer-patient relationship provides a solid basis for the treatment, which includes treatment for depression often associated with the disease, psychotherapy, discussions with Alcoholics Anonymous members, even drug treatment.

Coverage of therapeutic need
Today, three medicinal products have Marketing Authorisation in the maintenance of abstinence after withdrawal. There is no medicinal product with Marketing Authorisation in the reduction or ending of alcohol consumption. Therefore, providing drugs reducing the craving for and consumption of alcohol constitutes a therapeutic need in alcohol dependence[2].
From this point of view, SELINCRO is an option for this identified therapeutic need.

[1] RUEFF B. Maladies liées à la consommation d'alcool. *In: Traité de médecine.* Godeau P, Herson S, Piette JC. Médecine-Sciences, Flammarion, Paris, 4e édition, 2004; 1: 2658-71.
[2] European Medicines Agency, 18 February 2010 Guideline on the development of medicinal products for the treatment of alcohol dependence;
http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Several medicinal products have an indication in alcohol dependence:

Proprietary medicinal products concerned	Company	Indications
AOTAL 333 mg (acamprosate)	Merck Santé	Maintenance of abstinence in the alcohol-dependent patient. It should be combined with psychological support.
REVIA 50 mg (naltrexone)	Bristol-Myers Squibb	Support treatment in the maintenance of abstinence in alcohol-dependent patients. Naltrexone treatment can only be initiated after detoxification, and should be combined with psychological support.
ESPERAL 500 mg (disulfiram)	Sanofi	Adjuvant in the prevention of relapses during alcohol dependence.

Conclusion

There are no clinically relevant comparators for SELINCRO as all these proprietary medicinal products are indicated after achieving withdrawal.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
United Kingdom	YES (11/04/2013)	

08 ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and safety of SELINCRO is based on three phase III studies: the 12014A and 12023A studies of a similar study design, and the 12013A study. These studies were conducted within an outpatient context without any prior detoxification.

08.1 Description of the studies

Objectives	**12014A and 12023A studies:** Demonstrating the efficacy and safety of nalmefene 18 mg (1 tab a day as needed) versus placebo at 24 weeks, in conjunction with psychosocial support, in alcohol-dependent patients. **12013A study:** Demonstrating the efficacy of nalmefene 18 mg (1 caps a day as needed) versus placebo at 24 weeks, in conjunction with psychosocial support, in alcohol-dependent patients. Assessing its safety and tolerability at 56 weeks.
Method	**12014A and 12023A studies:** Controlled studies of nalmefene versus placebo, in conjunction with psychosocial support, randomised (ratio 1:1), double-blind, for a treatment duration of 24 weeks.

	So as to assess any symptoms of nalmefene withdrawal, the patients who ended the initial period of 24 weeks entered a 4-week, double-blind phase. The patients who initially received nalmefene were randomised again (ratio 1:1) to receive nalmefene or placebo; the patients who were already taking placebo continued. The visits took place at Weeks 1, 2, 4, 8, 12, 16, 20, 24 and 28, with an additional visit for safety follow-up at 32 weeks. **12013A study:** Controlled study of nalmefene versus placebo, in conjunction with psychosocial support, randomised (3:1), double-blind, for a follow-up of 1 year. The visits took place at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52, with an additional visit for safety follow-up at 56 weeks.
Main criteria for selection of patients	Inclusion criteria: • patients aged 18 years and over; • alcohol-dependent according to the DSM-IV classification; • number of heavy drinking days per month (≥ 60 g/day in men and ≥ 40 g/d in women) ≥ 6 • drinking risk level according to the WHO at least "medium" (see Table 1[3]) apart from in the 1-year study (12013A) for which patients with a "low" risk level could be included, but only for the safety analysis; • ≤ 14 consecutive days of abstinence in the 4 weeks preceding the screening visit; • ASAT and/or ALAT < 3 times the normal level; • absence of withdrawal symptoms requiring drug treatment (CIWA-Ar score < 10)[4] or a history of delirium tremens or epileptic seizure following alcohol withdrawal. Non-inclusion criteria, in particular: • patients with psychiatric disorders; • patients with liver, kidney or heart disease considered unstable.
Treatment methods	Study treatment The patients were randomised to receive nalmefene or placebo in conjunction with psychosocial support. In the event of exposure to the risk of drinking alcohol, the patient was to take the study treatment 1 to 2 hours before he anticipated the risk of consuming alcohol. If the patient had started to drink before taking the treatment, he was to take a tablet as quickly as possible. Maximum dose allowed = 1 tablet a day.
Concomitant therapies	Psychosocial support During the trial, all the patients received psychosocial support according to the BRENDA approach,[5][6] an approach based on motivational interviews, centred on the patient, with a focus on the patient's compliance and on reducing alcohol consumption.
Assessment parameter	The risk level on the WHO scale, the number of heavy drinking days and the total alcohol consumption were obtained using the Timeline Followback (TLFB) method.[7]

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Table 1: Drinking risk level according to the WHO in g/d

Risk level	**Total alcohol consumption (g/d)***	
	Men	**Women**
Low	1 to 40	1 to 20
Average	41 to 60	21 to 40
High	61 to 100	41 to 60
Very high	> 100	> 60

* 10 g of alcohol is equivalent to a “standard” drink (10 cl of wine at 12° or 25 cl of beer at 5° or 3 cl of whisky at 40°).

[4] Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. *Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar)*. Br J Addict 1989: 84; 1353-1357

[5] Starosta AN, Leeman RF, Volpicelli JR. *The BRENDA Model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders*. J Psychiatric Pract. 2006; 12: 80-89

[6] Volpicelli JR, Pettinati HM, McLellan AT, O’Brien CP (2001) Combining Medication and Psychosocial Treatments for Addictions: The BRENDA Approach. Guilford Press, New York.

	The TLFB is a method allowing the patient to estimate retrospectively, with the help of a calendar, the number of glasses drunk each day over a specified period. During the screening visit, the patients were to provide an estimation of their daily consumption over the previous 4 weeks. For the subsequent visits, the estimation was to cover the period since the previous visit.
Efficacy endpoint	**Primary efficacy endpoint** **Two co-primary efficacy endpoints were defined:** • Evolution of the **number of heavy drinking days per month** (Heavy Drinking Days, HDD), estimated by the TLFB, from baseline to Month 6. • Evolution of the **total alcohol consumption, in grams per day** (Total Alcohol Consumption, TAC), estimated by the TLFB, from baseline to Month 6. **Secondary endpoints, in particular:** - percentage of patients who have reduced their drinking risk level on the WHO scale, from baseline (screening visit) to Month 6. - percentage of patients who have dropped to the lowest drinking risk level on the WHO scale. - percentage of patients who have reduced their consumption by at least 70%.
Sample size calculation	An average difference of 3 days of heavy drinking between the groups (standard deviation 7 days) and 12 g/d of total alcohol consumption (standard deviation 36.5 g/d) was assumed, with a correlation coefficient between the two co-primary criteria of 0.7. Based on this hypothesis: - In the 12014A and 12023A studies, on the basis of a randomisation ratio of 1:1, 600 patients (300 per treatment group) were estimated as necessary to demonstrate that the SELINCRO group is statistically different from the placebo one with a power of 90%, a significance threshold of 5% and a percentage of premature treatment discontinuation of 35% at 6 months. - In the 12013A study, on the basis of a randomisation ratio of 3:1, 668 patients (167 placebo and 501 nalmefene) were estimated as necessary to demonstrate that the SELINCRO group is statistically different from the placebo one with a power of 90%, a significance threshold of 5% and a percentage of premature treatment discontinuation of 20% at 6 months.
Statistical analysis	The population for analysis was defined in three population groups: - all randomised patients: ITT population - all randomised patients excluding those who never received treatment or who returned all the tablets: modified ITT population - all randomised patients excluding those who never received the study treatment, with at least one post-baseline efficacy measure for the two primary endpoints during the 24 treatment weeks: FAS (full analysis set) population. All the efficacy analyses were carried out on the FAS population. The analysis of the co-primary endpoints (heavy drinking days and total alcohol consumption) was an analysis using a mixed model for repeated measures. The analysis of the effect at week 24 was the main analysis. This analysis was performed in the FAS population using observed cases (patients for whom the data were available at month 6). Several sensitivity analyses were performed to test the robustness of the results: analyses of covariance (ANCOVA) using OC (observed cases), LOCF (Last Observation Carried Forward) where the missing values were replaced by the last available value, BOCF (Baseline Observation Carried Forward) with, as a principle, the replacement of the missing value by the initial value and PMI (placebo mean imputation) where the missing values were replaced by the average value in the placebo group. An analysis of the co-primary endpoints in the subpopulation of patients with a high or very high drinking risk level maintained between screening and randomisationwas performed ***post-hoc***, using a mixed model for repeated measures (MMRM). A sensitivity analysis was performed with an ANCOVA model using LOCF. The secondary endpoints were analysed with a logistical regression model, taking into account the value at the screening visit, the sex, the country, the study concerned and the treatment as fixed effects. An amendment to the protocol was made to allow an analysis of the secondary endpoints from the grouped data of the 12014A and 12023A studies.

[7] Sobell LC, Sobell MB. *Timeline Follow-back: a technique for assessing self-reported ethanol consumption*. In: Litten RZ, Allen JP, editors. Measuring alcohol consumption: psychosocial and biological methods. Totowa, NJ, US: Humana Press; 1992. p 41-72

The statistical analysis plan pre-specified an analysis of the co-primary endpoints (heavy drinking days and total alcohol consumption in grams) and the percentage of patients who had reduced their risk level on the WHO scale[3] in the subpopulation of patients with a high or very high drinking risk level at the screening visit.
However, between selection and randomisation, a sharp reduction in alcohol consumption was observed in some patients (average consumption: 3 heavy drinking days per month and about 15 g/d for the total alcohol consumption). These patients were not considered in the analysis of the subpopulation as there was a slim chance they would improve further (floor effect). They could not therefore contribute to estimating the effect of nalmefene.

The results of the patient population (post-hoc analysis) **with a high or very high drinking risk level maintained between the screening visit and the randomisation visit** (consumption ≥ 60 g/day in men and ≥ 40 g/day in women) provided the rationale for granting the Marketing Authorisation (*see EPAR*[8]). This population represents about half of the total population included in the studies.

Overall study population
In total, 604 patients were randomised in the 12014A study (306 in the nalmefene group versus 298 in the placebo group), 718 in the 12023A study (358 vs 360) and 675 in the 12013A study (509 vs 166). At baseline, about 80% of patients in each of the studies had a "high or very high" drinking risk level according to the WHO classification and about 20% of patients had a "medium" risk level, that is an average of approximately 20 heavy drinking days per month (where 1 month = 28 days) and a total alcohol consumption of approximately 85 to 90 g/day on average.
Compared with the total study population, the distribution of the population with a high or very high drinking risk level is summarised in Table 2.

Table 2: Distribution of the patient population with a high or very high drinking risk level compared with the total population, FAS (Full analysis set) population

	Placebo N (%)	NMF N (%)	Total N (%)
12014A (6 months)			
Total population	289 (100%)	290 (100%)	579 (100%)
Population with a high or very high drinking risk level	167 (58%)	171 (59%)	338 (58%)
12023A (6 months)			
Total population	326 (100%)	329 (100%)	655 (100%)
Population with a high or very high drinking risk level	155 (48%)	148 (45%)	303 (46%)
12014A + 12023A Pool			
Total population			
Population with a high or very drinking risk level	615 (100%) 322 (52%)	619 (100%) 319 (52%)	1,234 (100%) 641 (52%)
12013A (1 year)			
Total population	137 (100%)	415 (100%)	552 (100%)
Population with a high or very high drinking risk level	42 (31%)	141 (34%)	183 (33%)

[8] SELINCRO: EPAR (European public assessment report). Available at: http://www.ema.europa.eu

The treatment was taken on average every other day. Across the three studies, the percentage of treatment discontinuation at month 6 was high, in the total population (40%) and also in the subpopulation with a "high or very high drinking risk level" (42%). The main reasons for discontinuing in this subpopulation were the withdrawal of consent (nalmefene = 15%, placebo = 13%) and the occurrence of an adverse event (nalmefene = 14%, placebo = 5%).

The characteristics of the population with a "high or very high" drinking risk level were similar to those in the total population:
The average age of the patients was 44 to 53 years according to the studies. Between 61 and 78% were men. The average age at the onset of the disorder was between 32 and 38 years of age and 26 to 41% of them had already been treated for their alcohol dependence.

Across all three studies, the patients drank on average 10 to 11 glasses a day and had between 19 and 23 heavy drinking days per month.
Between 40 and 60% of them had elevated GGT.

08.2 Results for the primary efficacy endpoints:

The population chosen for the analysis of the results is the FAS population: all randomised patients excluding those who never received study treatment, with at least one post-baseline efficacy measure in the two primary endpoints over 24 treatment weeks. The analysis was performed on the FAS population in the total population. There was no ITT analysis.
The results of the three studies for the two co-primary endpoints (number of heavy drinking days per month and total alcohol consumption per month) are presented in Tables 3, 4 and 5.

As a reminder: 10 g of alcohol is equivalent to a standard drink (10 cl of wine at 12° or 25 cl of beer at 5° or 3 cl of whisky at 40°).

In the overall study population (FAS analysis, observed cases),[9] the results showed:
In terms of the reduction in the number of heavy drinking days per month between the base value and the 6th month:
- superiority of nalmefene over placebo in two studies (12014A and 12023A studies),
- no difference between nalmefene and placebo in one study (12013A study).

In terms of the reduction in total alcohol consumption (in g/day) from baseline to month 6:
- superiority of nalmefene over placebo in one study (12014A)
- no difference between nalmefene and placebo in two studies (12023A and 12013A studies).

As a reminder, the statistical analysis plan pre-specified an analysis of the co-primary endpoints in the subpopulation of patients with a high or very high drinking risk level. However, between screening and randomisation, a large reduction in alcohol consumption was detected in some patients, who were not considered in the subpopulation analysis. The analysis of the results was therefore carried out on the subpopulation of patients who had maintained a "high or very high drinking risk level between screening and randomisation".
This *post-hoc* analysis showed that the effect of the treatment was more pronounced in this subpopulation of patients. The results of this population defined *a posteriori* (EPAR, p 34) as the target population for the Marketing Authorisation are presented for information.

Table 3: Results of the 12014A study, FAS (Full analysis set) population

[9] the FAS population only taking into account the patients for whom the data on alcohol consumption in the 6th month were available

	Total population		Patients with a high or very high risk (post-hoc analysis)*	
12014A study	**Nalmefene**	**Placebo**	**Nalmefene**	**Placebo**
Number of heavy drinking days per month (HDD in number of days/month)				
Primary analysis: FAS using observed cases [9] ***(MMRM)***	**N= 152**	**N= 213**	**N= 85**	**N= 114**
HDD in number of days/month at baseline, average (SD)	19.4 (7.3)	19.6 (6.9)	23.0 (5.9)	23.1 (5.4)
Reduction from baseline to month 6 (SD)	-11.2 (0.6)	-8.9 (0.6)	- 11.6 (1.0)	- 8.0 (1.0)
Difference vs placebo (SD), [95% CI], p vs placebo	- 2.3 (0.8) [-3.8; -0.8], p=0.002		- 3.7 (1.1) [-5.9; -1.5], p=0.001	
Sensitivity analysis: FAS using LOCF (ANCOVA)	**N= 290**	**N= 289**	**N= 171**	**N= 167**
HDD in number of days/month at baseline, average (SD)	19.4 (7.3)	19.6 (6.9)	23.0 (5.9)	23.1 (5.4)
Reduction from baseline to month 6 (SD)	-10.2 (0.6)	-8.4 (0.6)	- 10.6 (1.0)	- 7.6 (1.0)
Difference vs placebo (SD), [95% CI], p vs placebo	- 1.7 (0.7) [-3.0; -0.4], p=0.010		- 3.0 (1.0) [-4.8; -1.1], p=0.002	
Total alcohol consumption per month (TAC in g/d)				
Principal analysis: FAS using observed cases [9] ***(MMRM)***	**N= 152**	**N= 213**	**N= 85**	**N= 114**
TAC in g/d at baseline Average (SD)	84 (42)	85 (42)	102 (43)	99 (40)
Reduction from baseline to month 6 (SD)	-50.7 (2.4)	-39.7 (2.2)	-58.3 (4.1)	-40.0 (3.9)
Difference vs placebo (SD), [95% CI], p vs placebo	- 11.0 (3.0) [-16.8; -5.1], p<0.001		- 18.3 (4.4) [-26.9; -9.7], p<0.001	
Sensitivity analysis: FAS using LOCF (ANCOVA)	**N= 290**	**N= 289**	**N= 171**	**N= 167**
TAC in g/d at baseline Average (SD)	84 (42)	85 (42)	102 (43)	99 (40)
Reduction from baseline to month 6 (SD)	-46.5 (2.3)	-37.7 (2.3)	- 54.2 (4.1)	-37.8 (4.1)
Difference vs placebo (SD), [95% CI], p vs placebo	- 8.8 (2.8) [-14.3; -3.3], p=0.002		- 16.3 (4.0) [-24.2; -8.4], p<0.001	

*Population used by the Marketing Authorisation

Table 4: Results of the 12023A study, FAS (Full analysis set) population

	Total population		Patients with a high or very high risk (post-hoc analysis)*	
12023A study	**Nalmefene**	**Placebo**	**Nalmefene**	**Placebo**
Number of heavy drinking days per month (HDD in number of days/month)				
Principal analysis: FAS using observed cases [9] ***(MMRM)***	**N= 212**	**N= 229**	**N= 103**	**N= 111**
HDD in number of days/month at baseline, average (SD)	**19.8 (6.8)**	**18.3 (7.0)**	**22.7 (6.0)**	**21.6 (6.4)**
Reduction from baseline to month 6 (SD)	**-12.3 (0.5)**	**-10.6 (0.5)**	**- 12.9 (0.9)**	**- 10.2 (0.9)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 1.7 (0.7) [-3.1; -0.4], p=0.012**		**- 2.7 (1.2) [-5.0; -0.3], p=0.025**	
Sensitivity analysis: FAS using LOCF (ANCOVA)	**N= 329**	**N= 326**	**N= 148**	**N= 155**
HDD in number of days/month at baseline, average (SD)	**19.8 (6.8)**	**18.3 (7.0)**	**22.7 (6.0)**	**21.6 (6.4)**
Reduction from baseline to month 6 (SD)	**-11.8 (0.5)**	**-10.0 (0.5)**	**- 12.2 (0.9)**	**- 9.5 (0.9)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 1.8 (0.6) [-3.0; -0.6], p=0.004**		**- 2.7 (1.1) [-4.8; -0.6], p=0.013**	
Total alcohol consumption per month (TAC in g/d)				
Principal analysis: FAS using observed cases [9] ***(MMRM)***	**N= 212**	**N= 229**	**N= 103**	**N= 111**
TAC in g/d at baseline Average (SD)	**93 (46)**	**89 (48)**	**113 (48)**	**108 (47)**
Reduction from baseline to month 6 (SD)	**-59.0 (2.3)**	**-54.1 (2.2)**	**-70.4 (4.0)**	**-60.1 (4.0)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 5.0 (2.9) [-10.6; 0.7], NS**		**- 10.3 (5.0) [-20.2; -0.5], p=0.040**	
Sensitivity analysis: FAS using LOCF (ANCOVA)	**N= 329**	**N= 326**	**N= 148**	**N= 155**
TAC in g/d at baseline Average (SD)	**93 (46)**	**89 (48)**	**113 (48)**	**108 (47)**
Reduction from baseline to month 6 (SD)	**-57.6 (2.2)**	**-51.7 (2.2)**	**- 68.6 (3.9)**	**-57.7 (4.0)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 5.9 (2.6) [-11.1; -0.7], p=0.026**		**- 10.9 (4.6) [-20.0; -1.8], p=0.019**	

*Population used by the Marketing Authorisation

Table 5: Results of the 12013A study, FAS (Full analysis set) population

	Total population		Patients with a high or very high risk (post-hoc analysis)*	
12013A study	**Nalmefene**	**Placebo**	**Nalmefene**	**Placebo**
Number of heavy drinking days per month (HDD in number of days/month)				
Principal analysis: FAS using observed cases [9] ***(MMRM)***	**N= 320**	**N= 110**	**N= 102**	**N= 32**
HDD in number of days/month at baseline, average (SD)	**15.2 (6.1)**	**14.7 (6.1)**	**19.1 (6.3)**	**18.6 (6.4)**
Reduction from baseline to month 6 (SD)	**-9.8 (0.4)**	**-8.9 (0.6)**	**- 9.9 (0.9)**	**- 7.2 (1.4)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 0.9 (0.6) [-2.1; 0.4], NS**		**- 2.6 (1.5) [-5.5; 0.2], NS**	
Sensitivity analysis: FAS using LOCF (ANCOVA)	**N= 415**	**N= 137**	**N= 141**	**N= 42**
HDD in number of days/month at baseline, average (SD)	**15.2 (6.1)**	**14.7 (6.1)**	**19.1 (6.3)**	**18.6 (6.4)**
Reduction from baseline to month 6 (SD)	**-9.7 (0.4)**	**-9.0 (0.6)**	**- 9.2 (1.0)**	**- 6.8 (1.4)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 0.8 (0.6) [-2.0; 0.4], NS**		**- 2.4 (1.4) [-5.2; 0.4], NS**	
Total alcohol consumption per month (TAC in g/d)				
Principal analysis: FAS using observed cases [9] ***(MMRM)***	**N= 320**	**N= 110**	**N= 102**	**N= 32**
TAC in g/d at baseline Average (SD)	**75 (39)**	**75 (41)**	**100.4 (45.0)**	**100.6 (46.9)**
Reduction from baseline to month 6 (SD)	**-49.0 (1.6)**	**-45.6 (2.6)**	**- 56.7 (4.3)**	**- 41.4 (6.6)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 3.5 (2.9) [-9.2; 2.2], NS**		**- 15.3 (1.1) [-29.1; -1.5], p=0.031**	
Sensitivity analysis: FAS using LOCF (ANCOVA)	**N= 415**	**N= 137**	**N= 141**	**N= 42**
TAC in g/d at baseline Average (SD)	**75 (39)**	**75 (41)**	**100.4 (45.0)**	**100.6 (46.9)**
Reduction from baseline to month 6 (SD)	**-49.5 (1.8)**	**-45.5 (2.8)**	**- 53.0 (5.0)**	**-36.2 (7.2)**
Difference vs placebo (SD), [95% CI], p vs placebo	**- 4.0 (3.2) [-9.9; 2.0], NS**		**- 16.8 (7.2) [-31.0; -2.7], p=0.020**	

*Population used by the Marketing Authorisation

08.3 Results for the secondary efficacy endpoints:

In the assessment of the secondary endpoints in terms of responders (overall population and population with a high or very high risk):
- patients who have reduced their risk level by two categories or more on the WHO scale,
- patients who have shifted to the lowest risk level on the WHO scale,
- patients who have reduced their consumption by at least 70%,

nalmefene was superior to the placebo only in the 12014A study (*FAS analysis, MMRM*). Moreover, this superiority of nalmefene vs placebo does not appear in all sensitivity analyses.

The populations of the 12014A and 12023A studies were grouped for the analysis of these secondary efficacy endpoints. It was the same for the population who had a high or very high drinking risk level maintained between screening and randomisation. These results are presented for information and should be interpreted with caution **(Table 6)**.

Table 6: Grouped data from the 12014A and 12023A studies, FAS (Full analysis set) population

	Total population		**Patients with a high or very high risk (post-hoc analysis)***	
12014A and 12023A studies grouped:	**Nalmefene N= 619**	**Placebo N= 615**	**Nalmefene N= 319**	**Placebo N= 322**
Patients who have reduced their risk level by two categories or more on the WHO scale (RSDRL)				
FAS analysis (MMRM)	69%	61%	57%	42%
Odds Ratio, [95% CI], p vs placebo	1.49 [1.16; 1.91], p=0.002.		1.87 [1.35; 2.59], p<0.001.	
FAS, LREG (LOCF) analysis	65%	60%	52%	40%
Odds Ratio, [95% CI], p vs placebo	1.27 [1.00; 1.63], NS		1.63 [1.18; 2.25], p=0.003.	
FAS, NR analysis (missing values = failure)	42%	46%	34%	32%
Odds Ratio, [95% CI], p vs placebo	0.83 [0.66; 1.05], NS		1.14 [0.81; 1.60], NS	
Patients who have shifted to the lowest risk level on the WHO scale (RLDRL)				
FAS analysis (MMRM)	60%	55%	43%	32%
Odds Ratio, [95% CI], p vs placebo	1.36 [1.06; 1.75], p=0.017.		1.79 [1.27; 2.53], p<0.001.	
FAS, LREG (LOCF) analysis	58%	55%	40%	31%
Odds Ratio, [95% CI], p vs placebo	1.19 [0.93; 1.53], NS		1.58 [1.12; 2.23], p=0.009.	
FAS, NR analysis (missing values = failure)	37%	42%	27%	24%
Odds Ratio, [95% CI], p vs placebo	0.83 [0.65; 1.06], NS		1.23 [0.84; 1.79], NS	
Patients who have reduced their consumption by at least 70%				
FAS analysis (MMRM)	47%	41%	38%	26%
Odds Ratio, [95% CI], p vs placebo	1.31 [1.03; 1.67], p=0.030.		1.88 [1.32; 2.70], p<0.001.	
FAS, LREG (LOCF) analysis	44%	41%	37%	26%
Odds Ratio, [95% CI], p vs placebo	1.16 [0.91; 1.48], NS		1.75 [1.23; 2.52], p=0.002.	
FAS, NR analysis (missing values = failure)	30%	31%	25%	20%
Odds Ratio, [95% CI], p vs placebo	0.94 [0.73; 1.21], NS		1.44 [0.97; 2.13], NS	

*Population used by the Marketing Authorisation

08.4 Safety/Adverse effects

The population evaluated focuses on the grouped data of the overall population of the three studies - 12014A, 12023A, 12013A.

Treatment-emergent adverse events (TEAEs)
The incidence of adverse events was 75% in the nalmefene group versus 63% in the placebo group.
The frequent adverse events (observed with ≥ 5% frequency in either group) were nausea, dizziness and headaches (**Table 7**).
These events were more frequent in the nalmefene group than in the placebo group (apart from nasopharyngitis).

Table 7: Frequent adverse events – studies in alcohol dependence

		PBO		NMF
Term	**n**	**(%)**	**n**	**(%)**
Number of patients	797		1144	
Patients with TEAEs	500	(62.7)	855	(74.7)
Nausea	47	(5.9)	253	(22.1)
Dizziness	44	(5.5)	208	(18.2)
Insomnia	43	(5.4)	153	(13.4)
Headache	66	(8.3)	141	(12.3)
Nasopharyngitis	73	(9.2)	107	(9.4)
Vomiting	18	(2.3)	100	(8.7)
Fatigue	37	(4.6)	95	(8.3)
Somnolence	23	(2.9)	59	(5.2)

The incidence of adverse events considered "severe" was 14% in the nalmefene group versus 9% in the placebo group. Those with a frequency ≥ 1% were: nausea, dizziness, insomnia, headaches and vomiting.

The median time to onset of these adverse events as well as the median duration were shorter in the nalmefene group than in the placebo group. In the nalmefene group the time to onset was between 0 and 7 days after the first treatment.
These adverse events were transient. During the second month of treatment and in the following months, the incidence of these adverse events was lower than it was during the first month of treatment. No recurrence of these events was noted, regardless of the pattern of IMP intake.

The incidence and the profile of the adverse events were not different between the population with a "high or very high drinking risk level" (75% in the nalmefene group versus 62% in the placebo group) and the total population (modified ITT).

Adverse events leading to withdrawal

In total, 149 patients (13%) treated by nalmefene and 47 patients (6%) who received the placebo discontinued the treatment because of an adverse event. The adverse events leading to withdrawal with an incidence ≥ 1% in the nalmefene group were: nausea, dizziness, headaches and fatigue. In the placebo group, no adverse event led to withdrawal for at least 1% of patients.

The incidence of the adverse events leading to withdrawal were not different between the population with a "high and very high drinking risk level" (16.4% in the nalmefene group and 7.0% in the placebo group) and the total population (modified ITT).

Serious adverse events and death

Over all the studies, there were 4 deaths; 2 in the placebo group and 2 in the nalmefene group:
- 2 cases of suicide in the placebo group,
- 1 traumatic brain injury after a road traffic accident where the patient was a passenger in the nalmefene group,
- 1 sudden death (patient 61 years old) in the nalmefene group, cause of death not established.

The incidence of serious adverse events was similar in the two groups (5% versus 4%). Most of these events were found to be unrelated to the treatment by the investigator and rarely led to withdrawal(1.7% versus 1.5%).

The incidence and the profile of the serious adverse events were not different between the population with a "high or very high drinking risk level" (5.5% in the nalmefene group and 3.5% in the placebo group) and the total population (modified ITT).

Long-term safety
The adverse events profile in the 1-year 12013A study was similar to that observed in the six-month studies (12014A and 12023A studies).

European risk management plan
The risk management plan identifies the following important risks and missing information:

Important identified risks:
- Confusional state; hallucination, dissociation
- concurrent use with opioids

Important potential risk: off-label use (medium or low drinking risk level, alcohol use disorder without dependence)

Missing Information:
- specific populations (pregnant or lactating women, children, elderly)
- genetic polymorphism
- other ethnic groups than Caucasians
- overdose
- patients with transaminase levels (ALAT and ASAT) three times higher than normal (patients excluded from clinical trials)
- patients with a history of seizure disorder, including seizures linked to alcohol withdrawal
- patients with psychiatric comorbidities
- patients with somatic comorbidities, e.g. renal, hepatic, cardiac, neurological disorders
- long-term use (> 1 year)
- concurrent administration of other CNS-active medicines (antidepressants, antipsychotics, anxiolytics, hypnotics).

These risks and missing information will be covered by routine pharmacovigilance monitoring, as well as by three studies:
- a prospective, non-interventional cohort study in several European countries, with, as its objective, the provision of data on the conditions of use and the frequency of selected adverse events, in the total population treated and in subpopulations,
- a retrospective analysis of databases in several European countries,
- a pharmacokinetic study in patients with renal impairment.

The risk minimisation activities are routine activities (adequate information included in the Summary of Product Characteristics sections 4.2, 4.3, 4.4, 4.5, 4.8, 5.2, 5.3); no additional risk minimisation activities are required.

08.5 Summary & discussion

Nalmefene (1 tab/day as needed) was compared to placebo in three studies (12014A, 12023A and 12013A), for 6 months in the 12014A and 12023A studies and 1 year in the 12013A study. All the subjects also received psychosocial support.

The patients included were adults with alcohol dependence according to the DSM-IV classification who had various drinking risk levels (according to the Drinking Risk Level established by the WHO). A total of 604 patients were randomised in the 12014A study (306 in the nalmefene group versus 298 in the placebo group), 718 in the 12023A study (358 vs 360) and 675 in the 12013A study (509 vs 166). At baseline, about 80% of patients in each of the studies had a "high or very high" drinking risk level and about 20% had a "moderate" risk level. The average alcohol consumption was approximately 20 days of heavy drinking per month (in 28 days per month) and approximately 85 to 90 g/day.

Two co-primary efficacy endpoints were defined:
- reduction in the number of heavy drinking days per month (Heavy Drinking Days, HDD), from baseline to Month 6.
- reduction in total alcohol consumption, in grams per day (Total Alcohol Consumption, TAC), from baseline to Month 6.

The primary analysis was performed according to a mixed model for repeated measures (MMRM) on the FAS (Full analysis set, using observed cases) population, defined by all randomised patients, excluding those who had never taken the study treatment, with a post-baseline efficacy measure for the two primary endpoints at month 6. This analysis showed that:

In terms of the reduction in the number of heavy drinking days per month from baseline to month 6,
- nalmefene was superior to the placebo in two studies, but this difference is not clinically relevant:
  - -11.2 vs -8.9 d/month; p=0.002, i.e. difference of -2.3 d/month (12014A study)
  - -12.3 vs -10.6 d/month; p=0.012, i.e. a difference of -1.7 d/month (12023A study)
- nalmefene was not different to placebo in the third study:
  - -9.8 vs -8.9 d/month (12013A study)

The statistical analysis plan considered a difference of 3 days/month.

In terms of the reduction in total alcohol consumption (in g/day) from baseline to month 6,
- nalmefene was superior to the placebo in one study:
  - -50.7 vs -39.7 g/d; p<0.001, i.e. a difference of -11 g/d (12014A study). This difference is not clinically relevant.
- nalmefene was not different from the placebo in two studies:
  - -59.0 vs -54.1 g/d (12023A study)
  - -49.0 vs -45.6 g/d (12013A study)

The statistical analysis plan considered an absolute difference of 12 g/d.

A *post-hoc* analysis showed that the effect of the treatment was more pronounced in the subpopulation of patients **with a "high or very high drinking risk level maintained between screening and randomisation"** (consumption ≥ 60 g/d in men and ≥ 40 g/d in women). This population defined *a posteriori* therefore provided the rationale for granting the Marketing Authorisation (*see EPAR*[8]).

In this subpopulation with a high or very high drinking risk level maintained between screening and randomisation selected by the Marketing Authorisation, the primary analysis showed that:
In terms of the reduction in the number of heavy drinking days per month from baseline to month 6,
- nalmefene was superior to placebo in two studies (12014A and 12023A studies):

- -11.6 vs -8.0 d/month; p=0.001, i.e. a difference of -3.7 d/month (12014 A study)
- -12.9 vs -10.2 d/month; p=0.025, i.e. a difference of -2.7 d/month (12023A study)

- nalmefene was not different to placebo in one study:
  - -9.9 vs -7.2 d/month (12013A study)

In terms of the reduction in total alcohol consumption (g/day) from baseline to month 6,
- nalmefene was superior to the placebo in the three studies:
  - -58.3 vs -40.0 g/d; p<0.001, i.e. a difference of -18.3 g/d (12014A study)
  - -70.4 vs -60.1 g/d; p=0.040, i.e. a difference of -10.3 g/d (12023A study)
  - -56.7 vs -41.4 g/d; p=0.031, i.e. a difference of -15.3 g/d (12013A study)

Overall, the percentage of treatment discontinuation at month 6 was high, in the total population (40%) and also in the subpopulation with a "high or very high drinking risk level" (42%). The main reason for discontinuation in this subpopulation was the withdrawal of consent (nalmefene = 15%, placebo = 13%) followed by the occurrence of an adverse event (nalmefene = 14%, placebo = 5%).

The scope of the conclusions of these studies is limited by:
- the absence of an ITT analysis in these superiority studies, this particularly since the sensitivity analyses with imputation of missing data as "failure" (analysis close to an ITT analysis) did not show any difference between nalmefene and placebo on the secondary endpoints (patients who have reduced their drinking risk level by two categories or more on the WHO scale, patients who have shifted to the lowest drinking risk level on the WHO scale, patients who have reduced their consumption by at least 70%).
- transferability of the results that is not assured in real life. Indeed, the results of the subpopulation selected by the Marketing Authorisation are from a *post-hoc* analysis not only of the most severely affected patients, but also those from among them who are the most compliant, that is those for whom a value was recorded for the two primary endpoints at month 6 (FAS population using observed cases).

In total, the effect size observed with nalmefene (SELINCRO) in these studies is low in the subpopulation of patients with a "high or very high drinking risk level maintained between screening and randomisation" (consumption ≥ 60 g/day in men and ≥ 40 g/day in women), subject to psychosocial support and good compliance with the treatment.

Safety:
The safety profile was evaluated for all the patients of the three randomised studies, excluding those who never received treatment. In the nalmefene group compared with the placebo group:
- 75% vs 63% of patients reported at least one adverse event.
- The most frequent adverse events with a frequency of ≥ 5% were: nausea, dizziness, insomnia and headache.
- 13% vs 6% of patients withdrew due to an adverse event.
- The adverse events leading to withdrawal with an incidence ≥ 1% were: nausea, dizziness, headache and fatigue.

09 THERAPEUTIC USE

The treatment methods used in the treatment of primary alcohol dependence are hospitalisation, medicinal products, psychotherapy or associations, such as Alcoholics Anonymous. Employed simultaneously or consecutively in variable proportions, these treatments are suggested for treatment of a polymorphic disorder.
The three medicinal products available in France (acamprosate, naltrexone and disulfiram) have a Marketing Authorisation limited to the maintenance of abstinence after detoxification. No medicinal product has a Marketing Authorisation for the reduction or ending of alcohol consumption.
SELINCRO, in conjunction with psychosocial support, is a treatment option in the reduction of alcohol consumption in adult patients with alcohol dependence with a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. The potential benefit of the treatment depends on the patient's compliance.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

◗ Alcohol dependence is a serious disease, potentially life-threatening for the patient. Indeed, alcohol abuse was identified as a major risk factor in chronic diseases (mainly cancers, cardiovascular diseases, cirrhosis of the liver) and risk behaviours.[10]

◗ This medicinal product can be categorised as a curative therapy aiming to reduce excessive alcohol consumption in adult patients with alcohol dependence with a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. SELINCRO should be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment.

◗ The efficacy/adverse effects ratio is low.

◗ This medicinal product is a first-line therapy in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

◗ There are no treatment alternatives to this proprietary medicinal product with a Marketing Authorisation in this indication.

◗ Public health benefit:
The fight against excessive alcohol consumption is a priority in public health, with two objectives identified in the law relating to public health policy of 9 August 2004:

- reduce the average annual alcohol consumption per capita by 20% (from 10.7 litres per year and per capita in 1999 to 8.5 l/year/capita in 2008)
- reduce the prevalence of risky or harmful use of alcohol and prevent the onset of alcohol dependence.

These objectives have not been achieved, as noted by the HCSP [High Council for Public Health],[11] and the situation even seems to have taken a turn for the worse, particularly in young people and the socio-professional categories most at risk.

[10] Rehm J. *et al*. Alcohol and Global Health 1. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The Lancet 2009; 373: 2223-2233
[11] "Objectifs de santé publique: évaluations des objectifs de la loi du 9 août 2004 et propositions", HCSP, April 2010.

The government plan for fighting against drugs and addictive behaviour for 2013-2017 takes up the challenge of these objectives and sets the particular objective of "supporting research on new therapeutic strategies in the fight against addictive behaviour relating to alcohol."

The "chronic risk drinkers", defined by a daily consumption of between 3 and 7 drinks per day, represented 9% of 18-75 year olds and 14% of 18-24 year olds in 2010. This proportion of "chronic risk drinkers" has increased by 7.6% since 2005. The proportion of "drinkers at risk of dependence", defined by a consumption of more than 49 drinks per week, went from 0.9% in 2005 to 1.2% in 2010 (i.e. approximately 520,000 people) among 18-75 year olds.

The public health burden represented by excessive alcohol consumption is therefore considerable and the need for treatment is not currently covered, or not well enough.

The Société Française d'Alcoologie [French Society for the Study of Alcoholism] recalls in these different recommendations that the prescribing of a medicinal treatment, especially in the case of addictive behaviour, should always be done within the context of holistic care and that a medicinal treatment cannot be the only intervention in alcohol dependence. Psychosocial support remains at the heart of treatment for addictive behaviour.
There is a strong professional consensus for considering that psychological support provided by any trained therapist is the foundation of support for anyone struggling with alcohol.[12]

Beyond the effect, however small, of the medicinal product, excessive alcohol consumption should be managed holistically, and include psychosociological aspects. It is therefore important to ensure access to all recommended therapies for people who need it.

SELINCRO, through the possibility of implementing a strategy different from that of detoxification in the fight against excessive alcohol consumption, could contribute to providing a response to the public health need identified in alcohol-dependent patients with a high or very high drinking risk level. However, the data available provide little evidence to prove it. As a result, only a low public health benefit is expected for the proprietary medicinal product SELINCRO.

Taking account of these points, the Committee considers that the actual benefit of SELINCRO is <u>moderate</u> in the Marketing Authorisation indication.

The Committee recommends the inclusion of SELINCRO on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. " and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 30%**

010.2 Improvement in actual benefit (IAB)

In light of the available data, the Committee considers that SELINCRO, in conjunction with psychosocial support, provides a minor improvement in actual benefit (IAB IV) compared with psychosocial support alone in the treatment of alcohol dependence.

[12] Modalités de l'accompagnement du sujet alcoolodépendant après un sevrage, conférence de consensus ANAES-SFA, 2001

010.3 Target population

The target population of SELINCRO is made up of adult patients who have alcohol dependence with a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification.
In this population, SELINCRO should be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment.

The National Institute of Health and Medical Research (INSERM) estimates the number of people in France for whom their use of alcohol exposes them to medical, psychological and social problems to be five million, and the people who are alcohol-dependent to be two million.[13]

However, the population likely to receive SELINCRO treatment is much more restricted as this estimation does not take into account that:
- on the one hand, not all alcohol-dependent subjects are detected or cared for by the healthcare system;
- on the other hand, some patients will require immediate detoxification, others will choose the goal of reducing their consumption, and may therefore be eligible for SELINCRO.
For information only, according to a French opinion poll of the members of the SFA,[14] a third of practitioners estimate that at least half of their patients would choose the goal of reducing their alcohol consumption compared with the goal of abstinence, at least initially.

Moreover, in the 12013A study, which included alcoholic patients from all risk levels (low to very high risk), the percentage of patients with a high or very high risk level at baseline and who had maintained this risk level until randomisation was only 28% (187/ 655 randomised and treated patients).

Extrapolating from these data, we may estimate the target population at 280,000 patients maximum.

010.4 Transparency Committee Recommendations

◗ **This opinion depends on the applicant, together with leading centres for alcohol dependence, putting together an information sheet for prescribers defining the treatment methods: admission criteria, follow-up with systematic re-assessment at 6 months and discontinuation of the treatment. This sheet should be validated by the Haute Autorité de Santé [French National Authority for Health].**

◗ **Conditions for prescribing and use:**
Given the difficulty in transposing the results of the clinical trials to real life due, on the one hand, to the weakness in the effect size of this product and the frequent discontinuations (40%) of the treatment observed in the studies, and, on the other hand, the need for psychosocial support which GPs will not find feasible in general practice, the Committee recommends:

- Pursuant to articles L.5123-2 of the public health code and L.162-17 of the social security code, that the initial prescription of SELINCRO is restricted during the first year to addiction and alcohol specialists, the doctors from CSAPA or the doctors from hospital addiction units.

[13] Institut National de la Santé et de la Recherche Médicale (Inserm), *Alcool, dommages sociaux, abus et dépendance*, Collection expertise collective, Editions Inserm, 2003
[14] Luquiens et al, *Is Controlled Drinking an Acceptable Goal in the Treatment of Alcohol Dependence? A Survey of French Alcohol Specialists.* Alcohol 2011;46:586-91

- a real life follow-up of conditions for use of this product, and its impact on morbidity so as to proceed to a re-assessment in a year's time.

◗ Packaging:
Appropriate for the prescription conditions as regards the indication, dosage and treatment duration.