HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 April 2008

SUBOXONE 2 mg/0.5 mg, sublingual tablets, pack of 7 (CIP: 377 613-2) and pack of 28 (CIP: 377 614-9)
SUBOXONE 8 mg/2 mg, sublingual tablets, pack of 7 (CIP 377 615-5) and pack of 28 (CIP 377 616-1)

Applicant: SCHERING-PLOUGH

Buprenorphine/Naloxone

List I

Security prescription complying with the specifications fixed by the order of 31 March 1999.
Prescription restricted to 28 days. Dispensed in 7-day fractions.

Date of European MA (centralised procedure): 26 September 2006

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

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Buprenorphine/naloxone

1.2. Indication

"Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction."

1.3. Dosage

Treatment must be given under the supervision of a physician experienced in the management of opiate dependence/addiction.

Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product. Suboxone sublingual tablets are to be placed under the tongue until dissolved, which usually requires 5 to 10 minutes. The dose may require the use of Suboxone 2 mg/0.5 mg and Suboxone 8 mg/2 mg sublingual tablets, which may be taken all at the same time or in two divided portions; the second portion to be taken directly after the first portion has dissolved. […]

Institution of treatment:
The recommended starting dose is one to two tablets of Suboxone 2 mg/0.5 mg sublingual tablets. An additional one to two tablets of Suboxone 2 mg/0.5 mg may be administered on day one depending on the individual patient's requirement. […]
Patients receiving methadone: before beginning Suboxone therapy, the dose of methadone must be reduced to a maximum of 30 mg/day. The first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

Dosage adjustment and maintenance: The dose of Suboxone should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 24 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient and should be made in steps of 2-8 mg.
During the initiation of treatment, daily dispensing of buprenorphine is recommended.
After stabilisation, a reliable patient may be given a supply of Suboxone sufficient for several days of treatment. It is recommended that the amount of Suboxone be limited to 7 days or according to local requirements.

Less than daily dosing: After a satisfactory stabilisation has been achieved the frequency of Suboxone dosing may be decreased to dosing every other day at twice the individually titrated daily dose. […] However, the dose given should not exceed two 24 mg per day. In certain patients, after a satisfactory stabilisation has been achieved the frequency of Suboxone dosing may be decreased to 3 times a week. […]

Dosage reduction and termination of treatment: After a satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of the sublingual tablet in doses of 2 mg and 8 mg allows for a downward titration of dosage.
For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg sublingual tablets may be used. Patients should be monitored following termination of treatment because of the potential for relapse.

1.4. Pregnancy and breast-feeding

Suboxone should not be used during pregnancy. If it is the prescriber's opinion that therapy in pregnancy is required, the use of buprenorphine may be considered according to the local buprenorphine labeling.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (WHO, 2007)

N Nervous system
07 Other medicines for the nervous system
B Drugs used in addiction disorders
C Drugs used in opioid dependence
51 Buprenorphine in combination

2.2. Medicines with a similar therapeutic aim

Buprenorphine:

- SUBUTEX 0.4 mg, 2 mg and 8 mg, sublingual tablets (MA 31 July 1995)
- Buprenorphine hydrochloride generic group 0.4 mg, 2 mg and 8 mg:
  BUPRENORPHINE ARROW (marketed on March 2006),
  BUPRENORPHINE MERCK (marketed on April 2007)

List I

The use of a security prescription is required as specified in the Order of 31 March 1999.
Duration of prescription restricted to 28 days.
Dispensed in 7-day fractions.

Methadone:

- METHADONE HYDROCHLORIDE AP-HP 1.33 mg/ml, syrup (MA 17/01/2000), 5 mg/3.75 ml, 10 mg/7.5ml and 20 mg/15 ml, syrup (MA 21/03/1995), 40 mg/15 ml and 60 mg/15ml, syrup (MA 18/12/1995)
- METHADONE HYDROCHLORIDE AP-HP 1mg, 5mg, 10 mg, 20mg, 40mg, capsule (MA 20/09/2007)

Narcotic:

The use of a security prescription is required as specified in the Order of 31 March 1999.
Duration of prescription restricted to 14 days.
Dispensed in 7-day fractions.

The prescriber must write the duration of treatment corresponding to each fraction on the prescription.
However, under certain patient-specific situations, the prescriber may ask for the whole prescription to be dispensed a single time by writing "dispense in a single time" on the prescription.
When supplied by a dispensing pharmacist, where necessary the prescription may specify that it should be supplied on a daily basis by the pharmacist.

Medicinal product requiring initial six-monthly prescription by physicians practising in Specialised Drug Addict Care Centres (CSST) or physicians practising in healthcare establishments under the conditions specified by circular DGS/DHOS 2002/57 of 30/01/02.

Unrestricted renewal.
Medicinal product requiring specific monitoring during treatment

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. Comparative data versus buprenorphine

Randomised, double-blind study CR 96/013[1], compared the efficacy and safety of the combination of buprenorphine 16 mg/naloxone 4 mg per day with a placebo in opiate-dependant patients defined by DSM-IV criteria. The study comprised an active buprenorphine 16 mg/day arm.

Substitution treatment was instituted by buprenorphine 8 mg (D1) and 16 mg (D2). On D3, the patients received the treatment assigned by randomisation.

The primary efficacy endpoints were the number of opioid-negative urine samples and the score evaluating the opioid requirement of patients at 4 weeks of treatment.
326 patients with an average age of 38 years were randomised: Suboxone (n=110), Buprenorphine (n=106), Placebo (n=110).
The median duration of heroin dependence was 84 months (3 to 468 months). 50% of patients had already received a substitution treatment (methadone or laevo-alpha-acetyl-methadol).

Results

Percentage of opioid-negative urine samples at 4 weeks

Treatment	N	Negative samples	p vs Placebo[†]*
Buprenorphine/naloxone	109	17.8%	< 0.001
Buprenorphine	105	20.7%	< 0.001
Placebo	109	5.8%	-

[†] * Two-way ANOVA

Means scores evaluating the opioid requirement at 4 weeks

Treatment	N	Baseline values	Final values	p vs Placebo[†]*
Buprenorphine/naloxone	109	62.4	29.8	< 0.001
Buprenorphine	104	63.3	33.0	< 0.001
Placebo	109	65.6	55.1	-

[†] * Repeated-measures ANOVA

53/296 (18%) of patients prematurely stopped treatment; five patients including three on the combination stopped because of adverse events.
The most commonly reported treatment-related possibly events were: headaches (26% with buprenorphine/naloxone, 18% with buprenorphine, 12% with placebo), withdrawal syndrome (9%, 6%,18%), constipation (11%, 7%, 2%) and nausea (13%, 10%, 8%).

A safety follow-up study (study CR 96/014) was conducted over 52 weeks in 472 patients on buprenorphine/naloxone including 279 who took part in study CR 96/013. 385 patients received at least 8 weeks of treatment; 261 patients received at least 6 months of treatment. 24 patients prematurely stopped treatment (including 14 patients for adverse events). The most frequent of the 81 reported serious events was a rise in transaminase or lactate dehydrogenase levels which occurred in 10 patients (7 possibly treatment-related cases). The most frequently reported events were: headaches (43%) and withdrawal syndrome (41%).

1 Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Eng J Med 2003;349(10):949-58.

3.1.2. Comparative data versus methadone

The randomised, double-blind, Kakko[1] study compared the efficacy and safety of the combination of buprenorphine 16 mg/naloxone 4 mg per day with that of methadone 70 mg per day in heroin-dependant patients defined by DSM-IV criteria.

After a 24-day double-blind period of initiation of substitution treatment (methadone 90 mg or buprenorphine 16 mg/naloxone 4 mg), treatment could be modified according to predefined criteria (less than 3 missing visits, self-reported insufficient decrease of craving or self-reported withdrawal symptoms, any urine sample positive for illicit opiates and no signs of overdosing): stepping up of the methadone dose in 10-mg increments to 120 mg/day, the buprenorphine dose in 8 mg increments to 32 mg/day (switch to methadone 50 mg/day and increase in the dose up to 90 mg/day, if buprenorphine treatment was insufficient)

The primary efficacy endpoint was percentage patient retention in substitution treatment at 6 months. 96 patients with an average age of 35 years, were randomised: buprenorphine 16 mg/naloxone 4 mg (n=48), methadone 90 mg (n=48). The mean duration of opiate dependence was from 9 to 10 years.

Results

Number of patients receiving substitution treatment for 6 months

	Treatment Instituted	
	Buprenorphine 16 mg/naloxone 4 mg n=48	Methadone 90 mg n=48
Treatment discontinuation	11	10
No change of treatment	17	38
Switch to methadone	20	-

20/48 patients receiving buprenorphine/naloxone at the institution of substitution treatment had to switch to methadone.

Patients who completed the study with the instituted substitution treatment received on average 30 mg/day of buprenorphine (n=17) and 110 mg/day of methadone (n=38).

3.1.3. Substitution of Subutex treatment by Suboxone treatment

During an Australian study conducted in 17 patients, the switch from Subutex to Suboxone required an increase in the doses of buprenorphine for 14 patients.

The substitution of Subutex treatment by Suboxone treatment was studied in 64 patients during a Finnish retrospective study (RC050175). At baseline, nine patients were identified to be buprenorphine injectors. During the first 4 weeks, 53/64 patients remained on Suboxone (with the same buprenorphine dose for 46 of them). IV misuse of buprenorphine was observed in 6 to 7 patients per week.
At 4 months, 27/61 patients remained on Suboxone; the 5 patients who injected Suboxone at least once reported that they had felt no effect.

3.1.2. Finnish data on the use of the buprenorphine/naloxone combination

Subutex was introduced in Finland in 2002 and was dispensed under very strict control within the framework of maintenance treatment programs.

1 Kakko J. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependance: a randomised controlled trial. Am J Psychiatry 2007;164:1-7.

The study of H. Alho[1] describes and analyses the use and misuse of buprenorphine monotherapy and the buprenorphine/naloxone combination, introduced in Finland in 2004, in patients taking part in a syringe exchange program in the Helsinki region in April 2005. Data were obtained using a questionnaire distributed to drug addicts with a questionnaire return rate of only 30% (176/589).
For 73% of the persons who answered the questionnaire, buprenorphine was the substance the most frequently used by the IV route. 72% (113/157) reported multiple drug consumption.
68% (99/145) answered that they used the buprenorphine/naloxone combination by the IV route and 8.3% reported frequent or regular intravenous use.
13.5% of patients (15/111) reported sublingual use of the combination, 22% oral and IV use and 4.5% nasal use. Approximately 80% (86/107) of patients described the experience of the buprenorphine/naloxone combination as a bad experience and 20% as an experience similar to buprenorphine alone.

3.2. Safety data obtained during the development studies

1,631 of the 3,034 patients exposed to buprenorphine during clinical studies were exposed to the buprenorphine/naloxone combination. 1158 patients were followed up for 52 weeks. 175 of the 367 reported serious events occurred in patients receiving the buprenorphine/naloxone tablet combination (28 in patients taking buprenorphine tablets, 115 taking buprenorphine solution). The most commonly reported serious adverse events with this combination were hospitalisation for detoxification (34 patients), depression (14), abnormal hepatic tests (11) and overdosage (11).

4. NEW CLINICAL DATA SUBMITTED

4.1. Data on the North-American and Australian use of the buprenorphine/naloxone combination

a. Use and misuse of buprenorphine in the United States

Suboxone® and Subutex® were simultaneously made available in April 2003 in the United States.

Reckitt Benckiser Pharmaceuticals had to perform monitoring within the scope of a risk management program, including in particular: quarterly monitoring of doctors authorised to prescribe buprenorphine, a survey of patients entering for a program for the treatment of illicit substance dependence, an analysis of cases of overdoses and surveillance of cases reported by toxicology and emergency departments.
According to post-marketing follow-up data collected over 3 years by CRS Associates LLC (sponsored by Reckitt Benckiser Pharmaceuticals, Inc), the estimated number of patients receiving treatment at the end of Q1 2007 was 117,000 patients for Suboxone® and 12,000 patients for Subutex®.

Among the 12 to 21% of patients treated by buprenorphine for substance abuse by physicians answering the survey, 83 to 93% of the buprenorphine-treated patients monitored were receiving Suboxone. According to interview data from 624 patients included in a treatment program, the mean scores evaluating the abuse of medicines containing buprenorphine (Subutex®, Suboxone®) were lower than those of the other available opioids.
According to the surveillance network data on emergency department visits (between 2003 and 2006), the number of notifications mentioning Suboxone administration rapidly increased after marketing. The data obtained from drug addiction centres reported 93/519 cases of abuse and 53 cases of misuse with Suboxone®.

b. Use and misuse in Australia

In Australia, the conditions of prescription and supply of substitution treatments differ between federal States. In particular, regulations may encourage the prescription of the buprenorphine/naloxone combination to any new patient and only authorise outpatient treatment with the buprenorphine/naloxone combination.

1 Alho H., Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug and Alcohol Dependence 2007;88:75-78.

The buprenorphine/naloxone combination is available in Queensland since March 2006 (buprenorphine since March 2001, methadone since 1970). In this State, data on the use of substitution treatments show that methadone represents nearly 60% of the dose units of prescribed substitution treatment, buprenorphine 15% and the buprenorphine/naloxone combination 22%.
Data collected between December 2006 and October 2007 from the BHRC (Brisbane Harm Reduction Centre), the largest syringe exchange program in the state of Queensland, showed a peak in the number of injections of the buprenorphine/naloxone combination in March 2007 which was followed by a decrease and stabilisation. During this period, it accounted for 23% of all buprenorphine injections; the prescription of the buprenorphine/naloxone combination accounted for 59% of the buprenorphine dose units prescribed per month.

Within the scope of a NDARC[1] surveillance program, IDRS[2] data were collected from regular IV drug users. According to the data collected from the 907 questioned users, the number of buprenorphine injections increased between 2003 (8%) and 2007 (27%). During 2007, the proportion of regular users of injections (including buprenorphine/naloxone injections) decreased from 27% to 23%. Usage data differed between States. Intravenous misuse of the buprenorphine/naloxone combination may be lower and less common than that of buprenorphine alone. Recent injection of buprenorphine/naloxone was reported by 7% of regular users of injections.

4.2. Safety data

Data from three periodic safety update reports were submitted by Schering-Plough: One PSUR covering the period from 01.08.2004-31.03.2005 drafted by Reckitt Benckiser Healthcare (UK) and two European PSUR for the periods 26.09.2006-26.03.2007 and 27.03.2007-26.09.2007 drafted by Schering-Plough.

To date, no assessment report from a European rapporteur has been submitted to Afssaps.

Between 26 September 2006 and 26 March 2007, the estimated Suboxone exposure was approximately 57,499 patient-years (assuming a usual dosage of 8 mg/day). 442 adverse reaction reports were made over this period (194 patients). 156 (37%) of the 417 spontaneous reports were considered to be serious. 14 patients died. 21 cases of overdose and 39 cases of abuse or misuse were reported.

Between 27 March 2007 and 26 September 2007, the estimated Suboxone exposure was approximately 87,000 patient-years (assuming a usual dosage of 8 mg/day). The estimated number of patients exposed during clinical studies was 4,491. 715 adverse reaction reports were made over this period (334 patients). 120 (17%) of the 681 spontaneous reports were considered to be serious. 6 patients died.
Seven cases of overdose and eighteen cases of abuse or misuse were reported.

No variation to the SPC has been made since European product registration.

The purpose of the European risk management plan (RMP) for Suboxone is to describe the potential risks related to Suboxone use (overdosage, hepatic toxicity, follow up of the switch from Subutex to Suboxone, drug interactions, transmission of infectious agents, misuse, exposure during pregnancy and in the child) and the protocols of associated studies proposed by the firm, a pharmacovigilance plan and a risk minimisation plan.
Two clinical studies, requested by the CHMP, were included in the RMP:

- A randomised non-inferiority study to evaluate the proportion of patients present at the D3 visit after institution of Suboxone or Subutex substitution treatment in heroin-dependent patients.
- A randomised non-inferiority study to evaluate the percentage of patients not requiring dose escalation during a 7-day period of institution of treatment by Subutex or Suboxone in patients previously treated by Subutex.

1 National Drug and Alcohol Research centre

2 Illicit Drug Reporting System

Afssaps accompanied the marketing of the first Opioid Substitution Medications (OSM) with a specific pharmacovigilance and drug dependence follow-up, in particular using the tools of the CEIP[1]. Because of the increased offer of OSMs and the new intrinsic risks associated with methadone in solid form, Afssaps requested a risk management plan be set up at national level, for all OSMs.
As an adjunct to the RMP for each substitution drug, Afssaps plans to perform a survey to specifically evaluate the consequences of the marketing of new pharmaceutical forms or new substitution drugs such as Suboxone.

4.3. Conclusion

The efficacy of the sublingual buprenorphine/naloxone combination on opioid consumption of dependent patients was shown versus placebo.
The opioid type adverse reactions observed with buprenorphine were found with sublingual Suboxone.

Suboxone should not be used during pregnancy: this medicinal product should not therefore be used by women of childbearing age, in particular in precarious situations. Only Subutex and its generic drugs at the 0.4 mg dosage strength may be used in patients requiring dosages lower than 2 mg per day of buprenorphine.

Withdrawal symptoms caused by the intravenous administration of the buprenorphine/naloxone combination have been observed in heroin-dependent patients, patients stabilised with morphine and patients receiving methadone maintenance treatment[2]. The intensity of these symptoms varied according to the dose ratio between buprenorphine and naloxone and the patient's degree of dependency.

Suboxone, a drug intended to dissuade from intravenous misuse of buprenorphine, remains a potentially injectable substitution drug. The submitted clinical data show that this practice is still used by a significant number of the followed-up patients.

In patients stabilised by high-dose buprenorphine (HDB), withdrawal symptoms do not occur after occasional injection of the buprenorphine/naloxone combination[3,4].
Because of the very high affinity of buprenorphine for μ receptors and the short duration of action of naloxone, the stability and duration of the antagonist effect is open to question in buprenorphine-dependent patients frequently seen in France.

The Transparency Committee regrets the absence of a comparative study of the buprenorphine/naloxone combination versus buprenorphine to evaluate IV misuse of buprenorphine, in particular by injectors. In this latter case, it would be interesting to compare the buprenorphine/naloxone combination with methadone. There is also a lack of specific data about multiple-drug abusers and other types of misuse (sniffing, inhalation of smoke).

The data presented about the use and misuse of buprenorphine and the buprenorphine/naloxone combination show the changes in OSMs in the United States and Australia during recent years.

Taking into account differences in drug addiction management systems between these countries and France (OSM marketing history, regulations, guidelines), it is difficult to assess the potential positive impact of the marketing of Suboxone on the misuse of buprenorphine in France from these data, as this depends in particular on drug addiction treatment policy.

It is even more difficult to evaluate the impact of Suboxone on trafficking, taking into account the multiplicity of the factors that may affect the black market of substitution drugs, in particular the regulatory framework, prescription volume and HDB to Suboxone ratio, the general diversion potential of a substance and more generally addiction health policy.

---

1 French Centre for Evaluation and Information on Drug Dependence

2 Mendelson J et al. Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: why the ratio 4:1 ratio for treatment ? Drug and Alcohol dependence 2003;70:S29-37.

3 Vocci F, Ling W. Medications development successes and challenges. Pharmacol Ther 2005 10(1),93-108.

4 Harris DS et al. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilised on sublingual buprenorphine. Drug and Alcohol Dependence 2000, 61,85-94.

According to the current state of knowledge and taking into account the specific French use of opioid substitution treatments, the opinion of the “opioid substitution treatment"[1] group is reserved about the positive impact of Suboxone.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Opiate dependence may lead to symptoms of tolerance, withdrawal symptoms and all the psychological, behavioural and social consequences of the loss of control of consumption. Because of their addictive potency, these substances may cause fatal overdose. Drug injectors are at risk of infectious contamination (HIV and hepatitis C infections). The prevalence of concomitant mental disorders is very high.

The efficacy/safety ratio of Suboxone is high. The use of this medicinal product must be integrated within the framework of overall medical, social and psychological management.

There are alternative medications to this proprietary drug.

Public Health Benefit:

The public health burden represented by opiate dependence and the harmful consequences of IV injection of these drugs or diversion of substitution treatments is moderate.

The improved management of drug addiction is a public health need coming within the scope of established priorities (2007-2011 government drug addiction management and prevention plan; 2004-2008 governmental plan to combat illicit drug use, smoking and alcohol consumption; public health law etc). Suboxone only represents one component of this management which must be global and include medical, psychological and social measures.

The results of the available foreign studies cannot be extrapolated to a French setting as the conditions of prescription and supply of opioid substitution treatments, as well as methods for managing drug addicts, are different from one country to another. Also, it is currently impossible to assess to what extent Suboxone may reduce current misuse and in particular intravenous diversion of buprenorphine in France or the impact that this proprietary medicine may have on the harmful consequences of injection (transmission of HCV in particular). In addition, it is difficult in practice to identify those patients who may specifically benefit from this treatment.

This product may have an impact on society and on the health system though this will depend in particular on the way in which the coexistence of Suboxone and Subutex and its generic drugs is managed.

Consequently, although Suboxone potentially addresses a public health need, in the absence of any French data in particular about the reduction in IV injections compared to Subutex and the consequences of these injections, it is not expected to benefit public health.

The actual medical benefit of Suboxone in this indication is substantial.

1 Opinion of the TSO group adopted on 22 January 2008 by the Addictions Committee responsible for evaluating the implementation of measures of the 2007-2011 plan for the management and prevention of substance abuse and its efficacy.

5.2. Improvement in actual benefit

Taking into account the specific French use of opioid substitution treatments and the data in the dossier, the impact of the marketing of Suboxone in terms of buprenorphine misuse and trafficking remains to be determined. For this reason, the Transparency Committee considers that Suboxone does not improve actual benefit (IAB V) compared to Subutex and its generic drugs.

Suboxone provides an additional therapeutic tool for drug treatment of opiate dependency.

5.3. Therapeutic use

Two drugs are used for substitution treatment of opioid drug dependence: methadone and high dosage buprenorphine. This treatment must be integrated in a global approach that includes counselling with medical, psychological and social-educational follow-up and reintegration of the dependent person which all depend on close collaboration by a network of different institutions[1]. The success of pharmacotherapy mainly depends on the quality of psychotherapy and social intervention.

After its marketing in 1996, high-dose buprenorphine, which may initially be prescribed by any physician with no particular restrictions concerning the type of practice, very rapidly became the first treatment for opiate dependence in France in quantitative terms. Its very wide accessibility outside CSST[2] promoted the adoption of medical treatment and improved access to healthcare of heroin-dependent persons and reduced their medical and social risks.

The consensus conference held in June 2004[3] on therapeutic strategies for opiate-dependent persons concluded that the global risk reduction policy applied during recent years (freeing of sales and syringe exchange programs, setting up of the first low-threshold services, marketing of opioid substitution treatments) had been a success and that the opiate dependence treatment policy had had a positive impact of health and social problems. However it underlined the following factors:

. The system for obtaining access to healthcare and treatment was still too heterogeneous and unequal;
. The development of different forms of misuse;
. The maintenance or intensification of parallel substance abuse;
. The increased prevalence of hepatitis C contrasting with a decrease in HIV infection;
. The persistent stigmata of “drug addiction” despite treatment, the fact that psychological problems are not sufficiently taken into account.

The 2007-2011 addiction management and prevention plan[4] of aims in particular to:

- Better manage addiction in health care institutions by improving the organisation of this management and further developing health care management in these institutions;
- Improve management of drug addiction by community health centres through the creation of units offering healthcare and counselling for patients with all forms of substance abuse, and the continuation of the risk reduction policy (in particular by readjusting the offer between methadone and high-dose buprenorphine);
- Improve the coordination of care between general practitioners and health and medical-social structures, increase the involvement of office-based practise in the management of drug addiction, coordinate the clinical pathway of patients and improve collaboration between the legal and health systems;
- Develop prevention by promoting early detection and short interventions to modify behaviours and by reinforcing health education on drug addiction and the role of associations;
- Reinforce training of professionals in addictology by setting up permanent training structures in the field of addictology and integrating addictology during continuous training.

1 DGS/DHOS Circular n°2002/57 of 30 January 2002.

2 Specialised Drug Addiction Treatment Centre.

3 Therapeutic strategy for opiate-dependent persons: place of substitution treatments. Consensus conference, French Federation of addictology, with the participation of ANAES, 23-24 June 2004.

4 Management and Prevention of Substance Abuse - 2007-2011Plan - French Ministry of Health and Solidarity.

Currently, differences in the rules of prescription and disparities in the healthcare offer still considerably impact the choice of opioid substitution drug by patients and prescribers. However, methadone would be more particularly appropriate in the following cases:

. Severe dependence
. Difficulties in giving up injection
. Comorbid psychiatric disorders
. Multiple substance abuse (alcohol, BZD, cocaine, etc.)
. Highly precarious social situations
. Patients requiring treatment with opioid analgesics.

The buprenorphine/naloxone combination is an additional therapeutic tool for pharmacotherapy of opiate-dependent patients. Although it was designed to dissuade users from injection, this product is still diverted for IV use.
The potential therapeutic benefit of Suboxone may only be assessed on a case-by-case basis, mainly after the first prescription of buprenorphine in an injector patient informed about the specific features and limitations of this product, and desiring pharmacological treatment.

In the current French context, all measures for the generalised substitution of buprenorphine by the buprenorphine/naloxone combination are unnecessary and risky. In order to solve the problems raised by buprenorphine misuse a whole series of measures should be implemented in order to improve the quality of treatment follow-up ensured concomitantly with the prescription of a substitution drug.

5.4. Target Population

During 2005, heroin abuse concerned 0.2% of persons aged from 15 to 39 years (INPES, analysed by OFDT[1] December 2007) i.e. approximately 40,000 people.

According to Social Security reimbursement data, the estimated number of persons in France reimbursed during the first six months of 2007 for high dosage buprenorphine (BHD) and methadone was 96,956 and 22,863 respectively.
HDB accounts for 80% of substitution therapy. The proportion of patients receiving methadone has increased during recent years as improved access was one of the recommendations of the Consensus conference on substitution treatments in June 2004.
It should also be noted that since 2006, Subutex® is no longer the only available product as generic drugs have appeared on the market.

The total number of patients prescribed a substitution treatment by a CSST in 2005 may be estimated to be approximately 36,000 (slightly more than 19,000 for methadone and nearly 17,000 for HDB).

Although substitution treatments are generally taken within a medical framework, the increase in their availability has been accompanied by the development of misuse, mainly in the case of HDB: use outside a treatment regimen (self-substitution or misuse), use of a route of administration other than the planned route (injection or sniffing) or inappropriate doses or dangerous concomitant use with other substances, resale of all or part of the treatment.

Diversion of HDB for injection is increasing in the highly precarious population. At the same time, patients who have long received substitution therapy tend to divert by sniffing because of poor venous access and many new HDB consumers start consumption by the sniffing route as this is considered to leave fewer stigmata.

Seventy-two percent of patients in the 18 OPPIDUM 2006 survey[2], coordinated by the CEIP network, were receiving substitution treatment for opiate dependence within the framework of a medical protocol; this was HDB for 45% and methadone for 54%. 35% of all patients were taking HDB.

1 French Organisation of Drugs and Addictions

2 Observation of Illicit Use or Diversion of Psychotropic drugs - National pharmaco-epidemiological study, coordinated by the network of Centres for the evaluation and information on drug dependence (CEIP). 119 centres, 3743 analysable forms (Afssaps, October 2007)

In patients receiving HDB according to a medical protocol, the practise of sniffing is increasing and concerned 10% of these patients, whereas IV diversion is declining (10% of patients). For patients who said that they were taking HDB outside a medical protocol, 35 % diverted by sniffing and 30 % by the IV route. The use of heroin has increased (48%).

At the beginning of 2006[1] (national report of the TREND system[2], January 2007), purchase of HDB on the parallel market was the only or one of the modes of access for 41% of users seen in low-threshold structures who had taken HDB during the last month. 51% of these users reported exclusive or partial diverted use.
58% of recent users of HDB seen in low threshold structures (n=446) said that they had injected it during the last month. Diversion by sniffing was reported by 22% of these users.

Thirty-two per cent of recreational users of buprenorphine obtain it completely or partially by prescription. On the contrary, 16% of those who use it for substitution therapy (to stop or decrease heroin use) acquire it exclusively on the parallel market.

Although the misuse of methadone has become more apparent in parallel with its more widespread use, it remains low compared to that of HDB. In 2006, 29% of users seen in low-threshold units who had taken methadone during the last month said that they obtained it exclusively or partially on the black market. 29% of these users reported exclusive or partial diverted use. Less than 2% of methadone users said that they had injected it during the previous month.

The population of patients likely to benefit from improved management of their opiate dependence following the prescription of Suboxone remains to be determined.

5.5. Transparency Committee recommendations

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

5.5.1 Packaging

The packaging is appropriate to prescription requirements.

5.5.2 Reimbursement rate: 65%

1 PRELUD survey among users of first line structures (SPL) now called CAARUD (centres d'accueil et d'accompagnement à la réduction des risques des usagers de drogues) in 2006.

2 Recent trends and new drugs in France