HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
25 June 2014

STILNOX 10 mg, scored film-coated tablets

B/7 (CIP: 34009 339 036 1 9)
B/14 (CIP: 34009 346 585 7 0)
B/150 (CIP: 34009 563 132 0 4)

Applicant: SANOFI-AVENTIS FRANCE

INN	zolpidem
ATC Code (2013)	N05CF02 (hypnotic-benzodiazepine-like agent)

Reasons for the review	**Re-assessment of the Actual Benefit of benzodiazepine hypnotics and benzodiazepine-like agents at the request of the Committee, pursuant to Article R-163-21 of the French Social Security Code** **Renewal of inclusion on the list of medicinal products reimbursed by National Health Insurance**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"The indications are limited to severe sleep disorders in the following cases:** - **occasional insomnia,** - **transient insomnia. "**

Actual Benefit	**The actual benefit of the STILNOX proprietary medicinal products and generics is low in the treatment of "severe sleep disorders in the following cases: occasional insomnia, transient insomnia. "**
Recommendations	**The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indication "severe sleep disorders in the following cases: occasional insomnia, transient insomnia ".** **The Committee recommends:** - **better information for the public about the risks of chronic use of these medicinal products and their proper use through a powerful and repeated media campaign aimed at the general public,** - **enhancing the initial and continued training of healthcare professionals on the proper use of benzodiazepines and the methods for their discontinuation,** - **developing the use of and access to non-drug related treatments (cognitive behavioural therapy),** - **supporting measures which could be recommended by ANSM [French National Agency for Medicines and Health Products Safety] as part of its work which may enable improved used of these products.**

ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	09 June 1987 (national procedure)
Prescribing and dispensing conditions/special status	List I

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

Assessment Report
25 June 2014

CONTENTS

01 BACKGROUND AND OBJECTIVE OF THE RE-ASSESSMENT

01.1 Background

Benzodiazepines are medicinal products marketed since the 1960s which act on the central nervous system via GABA receptors. All benzodiazepines have varying degrees of anxiolytic, hypnotic, muscle relaxant and anticonvulsant properties. They are classified according to their indication as hypnotics for severe sleep disorders, anxiolytics for the symptomatic treatment of anxiety and alcohol withdrawal, antiepileptics, or anaesthetics. Two drugs marketed at the end of the 1980s, zolpidem and zopiclone, do not have the benzodiazepine chemical structure but are called "benzodiazepine-like agents" due to their mechanism of action and effects.

The adverse effects of benzodiazepines are well-known, in particular including memory disorders, reduced alertness or drowsiness, behavioural disorders and an increased risk of falls particularly in elderly patients.[1] The long-term use of benzodiazepines also results in a risk of pharmacological tolerance (gradual reduction of the therapeutic effect produced by the same administered dose) and psychological and physical dependence.
In addition, some studies suggest a possible link between the use of benzodiazepines and the long-term cognitive impairment.[2]

During the 1990s, several reports drew attention to the heavy use of benzodiazepines in France and the problem of their long-term use.[3,4] Since 1991, the maximum prescription duration has been limited to 4 weeks for hypnotics and 12 weeks for anxiolytics. Several actions aimed at limiting the use of benzodiazepines and promoting their proper use have been implemented on a national and local level: campaigns and information tools for the general public, information documents and good practice recommendations for healthcare professionals.[3,5]

In 2012 and 2013, the assessments of benzodiazepine use carried out by ANSM revealed that the prevalence of exposure to benzodiazepines remained stable between 2007 and 2012.[2,6] It is estimated at 11% of the population registered with National Health Insurance for benzodiazepine anxiolytics and 6.5% for benzodiazepine hypnotics or benzodiazepine-like agents.

In September 2012, the Ministry of Health, HAS and ANSM were engaged in a concerted action plan aimed at limiting the use of benzodiazepines and promoting their proper use.[7]

01.2 Objective

1 Summary of Product Characteristics (SPC) for benzodiazepine hypnotics and benzodiazepine-like agents.
2 AFSSAPS [French Healthcare Product Safety Agency]. Etat des lieux de la consommation des benzodiazépines en 2012. January 2012. www.ansm.sante.fr.
3 SFTG [Society for General Education in Therapeutics] HAS. Prise en charge du patient adulte se plaignant d'insomnie en médecine générale [Management of adult patients complaining of insomnia in general medicine]. December 2006. www.has-sante.fr.
4 Office parlementaire d'évaluation des politiques de santé. Rapport sur le bon usage des médicaments psychotropes [Report on the proper use of psychotropic drugs] June 2006. www.assemblee-nationale.fr.
5 HAS. Recommandations sur les modalités d'arrêt des benzodiazépines et médicaments apparentés chez le patient âgé [Recommendations on the methods for discontinuation of benzodiazepines and benzodiazepine-like agents in elderly patients]. 2007. www.has-sante.fr.
6 ANSM. Etat des lieux de la consommation des benzodiazépines en 2013. December 2013. www.ansm.sante.fr.
7 Communiqué de presse HAS - DGS - ANSM [HAS-Ministry of Health-ANSM Press release]. Des mesures contre le mésusage des benzodiazépines [Measures against the misuse of benzodiazepines]. September 2012. www.has-sante.fr.

At the time of the renewal of inclusion of several benzodiazepine hypnotics and benzodiazepine-like agents, at the request of the Ministry of Health, the Transparency Committee decided to re-assess their actual benefit (AB) in the management of sleep disorders, given the continued significant exposure of the population to benzodiazepines, the deleterious consequences posed by their short and long-term use and the data suggesting an association with the onset of dementia.

The re-assessment of other benzodiazepines is beyond the scope of this report.

01.3 Description of the proprietary medicinal products concerned

In France, 5 benzodiazepine hypnotics and 2 benzodiazepine-like agents are refundable for the short-term management of severe sleep disorders (see Table 1).
The maximum prescription duration for these proprietary medicinal products is limited to 4 weeks.

Table 1. Benzodiazepine hypnotics and benzodiazepine-like agents marketed in France

INN	Proprietary medicinal product	Mar.	Distributors of the originator medicinal product	Date of TC opinion	Level of AB
Benzodiazepines					
Estazolam	**NUCTALON**	1978	Takeda	17/01/2007	Moderate
Loprazolam	**HAVLANE**	1984	Sanofi-Aventis	17/01/2007	Substantial
Lormetazepam	**NOCTAMIDE**	1989	Bayer Santé	07/09/2011	Substantial
Nitrazepam	**MOGADON**	1966	Meda Pharma	31/03/2010	Moderate
Temazepam	**NORMISON**	1986	Alkopharm	--	Substantial[$]
Benzodiazepine-like agents					
Zolpidem	**STILNOX and generics**	1988	Sanofi-Aventis	17/01/2007	Substantial
Zopiclone	**IMOVANE and generics**	1987	Sanofi-Aventis	21/07/2010	Substantial

[$] Inclusion on the list of refundable medicines on 26 November 2003 replacing the previous presentations without submission to the Transparency Committee
Mar. : year of marketing; INN: International Nonproprietary Name

Benzodiazepine hypnotics and benzodiazepine-like agents are mainly distinguished by their pharmacokinetics (see Table 2).

Table 2. Tmax and ½ life of benzodiazepine hypnotics and benzodiazepine-like agents[3]

INN	Proprietary medicinal product	Tmax	½ life
Estazolam	**NUCTALON**	15-30 min	8-24 h
Loprazolam	**HAVLANE**	1 h	8 h
Lormetazepam	**NOCTAMIDE**	3 h	10 h
Nitrazepam	**MOGADON**	2-3 h	16-48 h
Temazepam	**NORMISON**	45 min-4 h	5-8 h
Zolpidem	**STILNOX and generics**	30 min	1.5-4.5 h
Zopiclone	**IMOVANE and generics**	1.5-2 h	5 h

02 LITERATURE SEARCH

02.1 Data identified in the literature

A literature search of data published between 01/01/2008 and 01/09/2013 was carried out in the Medline and Cochrane Library databases in order to find:

- meta-analyses, literature reviews and clinical studies evaluating the efficacy of benzodiazepine hypnotics and benzodiazepine-like agents in the short-term management of severe sleep disorders;
- meta-analyses, literature reviews and epidemiological studies evaluating the risks associated with taking benzodiazepines and benzodiazepine-like agents.

02.2 Data submitted by the pharmaceutical companies

The distributors were requested to supply HAS with all clinical information that would enable AB reassessment of benzodiazepine hypnotics and benzodiazepine-like agents.

02.3 Other sources

- Website and information provided by ANSM www.ansm.sante.fr;
- The European Medicines Agency (EMA) website www.ema.europa.eu;
- The US Food and Drug Administration (FDA) website www.fda.gov;
- The National Institute for health and Care Excellence (NICE) website www.nice.org.uk.

03 CLINICAL EFFICACY DATA

03.1 Review of the SFTG-HAS summary

In 2006, the Society for General Education in Therapeutics (SFTG) in partnership with HAS, published recommendations on the management of insomnia in adults in general practice.[3] The main data on the efficacy of benzodiazepines and benzodiazepine-like agents in the treatment of insomnia identified as part of the SFTG-HAS review are reported here.
No new data on the efficacy of benzodiazepines and benzodiazepine-like agents in the short-term management of insomnia have been identified since 2006.

3.1.1 Efficacy in relation to a placebo

Two meta-analyses comparing the efficacy of benzodiazepines to a placebo were selected:
- one meta-analysis by Nowell *et al.*[8] who evaluated the efficacy of 6 benzodiazepines and zolpidem in patients aged 65 years or under;
- one meta-analysis by Holbrook *et al.*[9] who evaluated the efficacy of 12 benzodiazepines and zopiclone in relation to a placebo.

The meta-analysis by Nowell *et al.* included 22 randomised studies comparing the short-term efficacy (average of 12 days) of 6 benzodiazepines and zolpidem in relation to a placebo in patients aged 65 years or under.
The studied medicines (number of studies) were: flurazepam (7), estazolam (4), zolpidem (4), triazolam (3), quazepam (3), temazepam (2), lorazepam (2).
The studied parameters were sleep onset latency, number of awakenings during the night, total sleep time and sleep quality. These parameters were measured subjectively (questionnaires and sleep diaries) and, for six studies, objectively (polysomnography). Effects on well-being and functional status during the day were not measured.
Benzodiazepines and zolpidem were significantly more effective than the placebo ($p < 0.001$) for all the studied parameters.
The effect sizes according to the Cohen criterion were moderate.[10]

The meta-analysis by Holbrook *et al.* included 45 randomised studies comparing the short-term efficacy (maximum of 6 weeks) of 12 benzodiazepines and zopiclone in relation to a placebo in 2672 patients.
The studied compounds (number of studies) were: triazolam (16), flurazepam (14), temazepam (13), zopiclone (13), midazolam (5), nitrazepam (4), estazolam (2), lorazepam, diazepam, brotizolam, quazepam, loprazolam, flunitrazepam.
The studied parameters in the studies were diverse, measured subjectively (sleep onset latency, total sleep time etc.) and objectively (polysomnography).
The main efficacy results of the benzodiazepines in relation to the placebo were as follows:
- superior efficacy of the benzodiazepines in relation to the placebo on sleep onset latency evaluated subjectively (8 studies; 539 patients; + 14.3 min; 95% CI [10.6; 18.0]) but no

[8] Nowell PD et al. Benzodiazepines and zolpidem for chronic insomnia - a meta-analysis of treatment efficacy. JAMA 1997; 278: 2170-2177.
[9] Holbrook AM et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000; 162: 225-33.
[10] The interpretation of the effect size proposed by Cohen *et al.* corresponding to the standardised difference between two averages is usually as follows: 0.2 = small effect; 0.5 = medium effect; 0.8 = large effect.

difference between the benzodiazepines and the placebo on sleep onset latency evaluated objectively (4 studies; 159 patients; + 4.2 min; 95% CI [- 0.7; 9.2]);
- superior efficacy of benzodiazepines in relation to the placebo on sleep time evaluated subjectively (8 studies; 566 patients; + 48.4 min; 95% CI [39.6; 57.1]) and objectively (2 studies; 35 patients; + 61.8 min; 95% CI [37.4; 86.2]);

3.1.2 Comparative efficacy of benzodiazepines and benzodiazepine-like agents

Two systematic reviews comparing the efficacy of benzodiazepines and benzodiazepine-like agents were selected:
- one review by Holm and Goa[11] of studies that compared zolpidem with other benzodiazepines and zopiclone;
- a systematic review by the Liverpool Group published by NICE[12] which compared the efficacy of benzodiazepine-like agents, with each other and with benzodiazepines, in the short-term management of insomnia.

Only the Liverpool Group results, which had a better methodological quality than Holm and Goa, are reported here.

In this systematic review, the efficacy of benzodiazepine-like agents (zolpidem, zopiclone, zaleplon) in the treatment of insomnia was evaluated in the short-term. The authors chose 24 randomised studies (3909 patients) comparing benzodiazepine-like agents with each other (7 studies) or with benzodiazepines (17 studies). The study duration ranged from 1 night to 6 weeks.
The studied parameters were sleep onset latency, number of awakenings during the night, total sleep time, sleep quality as well as the incidence of adverse effects during the day, daytime alertness and the rebound effect. Three studies included polysomnography recordings, all the other studies used subjective evaluation methods (sleep questionnaires and diaries). The main results are summarised in Table 3.

Table 3. Results of the comparisons between active treatments (Liverpool report[12])

Comparisons	Sleep parameters				Residual effects	Daytime alertness Rebound effect	
	Sleep onset latency	Nocturnal awakenings	Total time	Quality			
Zolpidem vs nitrazepam (n.2)	NS (n.2)	Z > N (n.1)	NS (n.1)	NDC (n.1)			
Zolpidem vs temazepam (n.2)	Z > Te (n.1) NS (n.1)	-	NDC (n.1)	Z > Te (n.1)	NS (n.1)	NS (n.1)	NDC (n.1)
Zopiclone vs lormetazepam (n.1)	L > Zop	NS	NS	NS	NS	-	-
Zopiclone vs nitrazepam (n.8)	NS (n.3) Zop > N (n.2) NDC (n.1)	NS (n.6) Zop > N (n.1)	NS (n.6) Zop > N (n.1)	NS (n.5) Zop > N (n.1) NDC (n.1)	NS (n.2) NDC	Zop > N (n.4) NS (n.3)	NDC (n.2)
Zopiclone vs temazepam (n.4)	NS (n.2) NDC (n.2)	NS (n.1) NDC (n.2)	NS (n.1) NDC (n.1)	NS (n.2)	NS (n.1) NDC (n.1)	NS (n.3) NDC (n.1)	Zop > Te (n.1) NS (n.1)
Zopiclone vs zolpidem (n.1)	Z > Zop	-	-	-	Zop > Z	NDC	Zop > Z

Z: zolpidem; N: nitrazepam; Te: temazepam; L: lormetazepam; Zop: zopiclone.
The numbers in brackets (n.1) designate the number of studies involving each comparison

[11] Holm KJ, Goa KL. Zolpidem - An update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. Drugs 2000; 59: 865-889.
[12] National Institute for Clinical Excellence. Liverpool Reviews and Implementation Group. Insomnia assessment report. 2004. www.nice.org.uk.

NS = not significant; NDC = No direct comparison between products.

The data does not support a conclusion of an efficacy difference between benzodiazepine-like agents and benzodiazepines. The few comparisons available on residual daytime effects, alertness and the rebound effect when treatment is discontinued also do not support a conclusion of a difference between the products.

3.1.3 Conclusion

The efficacy of benzodiazepine hypnotics and benzodiazepine-like agents (zolpidem and zopiclone) has been demonstrated in relation to a placebo in the treatment of insomnia, mainly in subjective sleep evaluations. The quantity of effect is low, around one extra hour of sleep. This evaluation was performed over a very short period (between 1 night and 6 weeks).

The data does not support a conclusion of an efficacy difference between the compounds. The few comparisons available on residual daytime effects, alertness and the rebound effect when treatment is discontinued also do not support a conclusion of a difference between the products.
The studies which compared benzodiazepine hypnotics or benzodiazepine-like agents with each other are mostly old and of low methodological quality. In addition, the variability of the studied parameters and the low number of available studies for each comparison makes interpretation of the results difficult.

04 ADVERSE EFFECTS

04.1 Main adverse effects

According to the SPCs, the main adverse effects associated with the use of benzodiazepines and benzodiazepine-like agents are:[1,2]

Anterograde amnesia	Memory loss of recent events can occur at therapeutic doses. The risk increases proportionally with the dose.
Reduced alertness	This can occur during the hours following administration.
Behavioural disorders	In some people, a syndrome associating varying degrees of behavioural disorders, memory loss and an impaired state of consciousness can occur. The following effects can therefore be observed: exacerbated insomnia, nightmares, agitation, nervousness, delusions, hallucinations, confusional and oniric state, psychosis-type symptoms, disinhibition with impulsivity, euphoria, irritability, suggestibility etc. This syndrome can be accompanied by potentially dangerous disorders for the patient or for others such as unusual behaviour, violent behaviour, particularly if those around the patient try to hinder the patient's activity, and automatic behaviours with amnesia after the event. These events require discontinuation of the treatment.
Pharmacological tolerance	Pharmacological tolerance is characterised by a gradual reduction in the therapeutic effect produced by the same administered dose; this occurs over several weeks. It can result in increased doses being required to maintain the desired effect.
Dependence	Benzodiazepines and benzodiazepine-like agents can cause physical and psychological dependence. Various factors appear to promote the occurrence of dependence: treatment duration, dose and a history of other drug- or non-drug-related dependencies, including alcohol dependence. Dependence can nevertheless occur at therapeutic dosages and/or in patients without any particular risk factors. The combination of several benzodiazepines, regardless of the indication, can increase the risk of dependence.
Withdrawal syndrome	Discontinuation of treatment with a benzodiazepine or benzodiazepine-like agents, even at normal doses, can result in withdrawal phenomena. Headaches, pains and muscle weakness, nightmares, irritability, agitation, tremors, anorexia, nausea, sweating, and diarrhoea may be observed. More severe manifestations can occur: convulsions, mood changes, depression, depersonalisation, temporal and spatial disorientation, hallucinations, and paranoid psychosis. Withdrawal syndrome must be distinguished from the rebound phenomenon which is transient and characterised by worsening of the symptom which led to treatment with a benzodiazepine or a benzodiazepine-like agent (rebound anxiety or insomnia).
Adverse effects in elderly patients	Benzodiazepines and benzodiazepine-like agents must be used with caution in elderly patients due to the risk of sedation and/or muscle relaxant effects which can promote falls, often with severe consequences in this population, and due to the higher frequency of behavioural disorders.

04.2 Specific risks

4.2.1 Falls

In 2007, HAS[5] carried out a review of studies which evaluated the association between exposure to benzodiazepines and the risk of falls in elderly patients. Eleven studies were selected:

- five cohort studies[13,14,15,16,17] revealed an increased risk of falls in patients exposed to benzodiazepines. This increase was more significant in elderly patients (OR between 2.2 and 2.7 for patients aged 80 years and over) and in recent users of benzodiazepines (OR between 2.0 and 3.6 for patients exposed during the 7 days before the fall);
  The impact of the half-life on the risk of falls was contradictory depending on the studies: two studies[13,15] revealed an increased risk with compounds with a short half-life (OR = 1.9 if < 6 hours, OR = 1.4 to 1.8 if half-life between 12 and 24 hours); the risk did not reach statistical significance if the half-life was longer than 24 hours. Two other studies[16,17] revealed a higher risk if the half-life was long (OR = 1.3 with a short half-life *versus* OR = 1.7 with a long half-life);
- five case-control studies[18,19,20,21,22] revealed an increased risk of falls in elderly patients exposed to benzodiazepines (OR = 2.2 to 2.7);
- One meta-analysis[23] concluded that there was a 48% higher risk of falls in patients aged 65 years or over exposed to benzodiazepines in comparison with non-exposed patients (OR = 1.48; 95% CI [1.23 to 1.77]).

Since 2007, three new studies evaluating the association between exposure to benzodiazepines or benzodiazepine-like agents and the risk of falls have been published:

- one cohort study by Berdot *et al.*[24] evaluated the association between inappropriate use of medicinal products and the risk of falls in 6.343 patients aged 65 years or over included in the "Three Cities" cohort. This study reveals an increased risk of falls in regular and occasional users of benzodiazepines with a long half-life (OR = 1.4; 95% CI [1.1 to 1.8]). This association was not revealed for compounds with a short half-life;

[13] Neutel CI et al. New evidence on benzodiazepine use and falls: the time factor. Age Ageing 1996; 25: 273-8.
[14] Maxwell CJ et al. A prospective study of falls after benzodiazepine use: a comparison of new and repeat use. Pharmacoepidemiol Drug Saf 1997; 6: 27-35.
[15] Passaro A et al. Benzodiazepines with different halflife and falling in a hospitalized population: The GIFA study. Gruppo Italiano di Farmacovigilanza nell'Anziano. J Clin Epidemiol 2000; 53: 1222-9.
[16] Ray WA et al. Benzodiazepines and the risk of falls in nursing home residents. J Am Geriatr Soc 2000; 48: 682-5.
[17] Landi F et al. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. J Gerontol 2005; 60: 622-6.
[18] Ryynänen OP et al. Medications and chronic diseases as risk factors for falling injuries in the elderly. Scand J Soc Med 1993; 21: 264-71.
[19] Gales BJ et al. Relationship between the administration of selected medications and falls in hospitalized elderly patients. Ann Pharmacother 1995; 29: 354-8.
[20] Caramel VMB et al. Benzodiazepine users aged 85 and older fall more often. J Am Geriatr Soc 1998; 46: 1178-9.
[21] Frels C et al. Iatrogenic causes of falls in hospitalised elderly patients: a case-control study. Postgrad Med J 2002; 78(922): 487-9.
[22] Pariente A et al. Benzodiazepines and injurious falls in community dwelling elders. Drugs Aging. 2008; 25(1): 61-70.
[23] Leipzig RM et al. Drugs and falls in older people: a systematic review and metaanalysis. Psychotropic drugs. J Am Geriatr Soc 1999; 47: 30-9.
[24] Berdot S et al. Inappropriate medication use and risk of falls - a prospective study in a large community-dwelling elderly cohort. BMC Geriatrics 2009; 9:30. July 23.

- one study by Strien *et al.*[25] evaluated the association between the use of psychotropic medications and the risk of falls in 404 elderly patients admitted into geriatric day hospitals in the Netherlands between January 2011 and April 2012. This study reveals an increased risk of falls in patients exposed to benzodiazepines with a short half-life (OR = 1.94; 95% CI [1.10 to 3.42]). This association was not revealed for benzodiazepines with a long half-life;
- one study by Obayashi *et al.*[26] retrospectively evaluated the risk of falls linked to hypnotics in 3.683 hospitalised patients over a 3-month period. In this study, the hypnotics are a risk factor for falls (OR = 2.17; 95% CI [1.44 to 3.28]). Amongst the hypnotics, zopiclone and estazolam were associated with an increased risk of falls in hospitalised patients in contrast to zolpidem and nitrazepam. However, given the number of patients treated with estazolam (31 of the 1306 patients treated with a hypnotic), these data are to be interpreted with caution.

In conclusion, the studies reveal an increased risk of falls in patients exposed to benzodiazepines or benzodiazepine-like agents, in particular in elderly patients. The impact of the compounds elimination half-life on the risk of falls is not clearly established; the results of the studies are contradictory.
The main methodological limits of the studies that evaluated the association between exposure to benzodiazepines or benzodiazepine-like agents and falls are:
- the lack of distinction between falls during the day and at night;
- the fact that the time of benzodiazepine administration is not taken into account;
- the fact that the associated diseases and/or treatments which could cause a fall are not taken into account.

4.2.2 Road traffic accidents

In 2007, HAS carried out a literature review[5] of the studies that evaluated the risk of road traffic accidents associated with taking benzodiazepines. The results of the six selected studies were contradictory:
- of the three cohort studies, one study[27] concluded that there was no association between taking benzodiazepines and the occurrence of accidents. A positive association between taking benzodiazepines and the occurrence of accidents was revealed in the other two studies.[28,29] Amongst these two studies, one[28] revealed an increased risk of accidents for high doses (risk multiplied by 2.4 for doses higher than or equal to 20 mg diazepam equivalent) and the other revealed an increased risk for the compounds with a long half-life (> 24 hours) and low exposure durations (OR = 1.45; 95% CI [1.04 to 2.03] for exposure < 7 days and OR = 1.26; 95% CI [1.09 to 1.45] for exposure > 60 days);
- of the two case-control studies, in one study[30] no association was found between taking benzodiazepines and the risk of accidents (RR = 1.5; 95% CI [0.6 to 3.8]). In the other study,[31] there was an increased risk of accidents for patients aged 45 years and under, as well as an increased risk for compounds with a short half-life;

[25] van Strien AM et al. Psychotropic medications, including short acting benzodiazepines, strongly increase the frequency of falls in elderly. Maturitas. 2013; 74: 357-62.
[26] Obayashi K et al. Risk of falling and hypnotic drugs: retrospective study of inpatients. Drugs R D. 2013; 13: 159-64.
[27] Soderstrom CA et al. Benzodiazepine use and crash risk in older patients [letter]. JAMA 1998; 279(2): 114-5.
[28] Ray WA et al. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. Am J Epidemiol 1992; 136: 873-83.
[29] Hemmelgarn B et al. Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 1997; 278(1): 27-31.
[30] Leveille SG et al. Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology 1994; 5: 591-8.
[31] Barbone F et al. Association of road-traffic accidents with benzodiazepine use. Lancet 1998; 352(9137): 1331-6.

- a cross-sectional study by Johansson *et al.*[32] did not support a conclusion of an association between taking benzodiazepines and the occurrence of road traffic accidents.

In 2011, a retrospective cohort study[33,34] supported by ANSM, based on data collected by the police during road traffic accidents and on data from medicine refunds by Health Insurance (SNIIRAM [National system of information between health insurance plans]), revealed an increased risk of accidents in 3843 drivers presumed to have been exposed to benzodiazepines or benzodiazepine-like agents (OR = 1.20; 95% CI [1.10 to 1.31]). This association was not revealed for the benzodiazepine-like agents.

The divergence of the results from these studies reflects their methodological heterogeneity (method of subject enrolment, chosen efficacy endpoints etc.) and the limits of most of them:
- The lack of information about comorbidities (cardiovascular disorders, visual, hearing, osteoarticular, neurological, cognitive or depressive disorders etc.) or the reason for prescription of the benzodiazepines or benzodiazepine-like agents and/or the associated treatments;
- the lack of information about possible associated alcohol consumption;
- the impossibility of distinguishing what pertains to the actual effect of benzodiazepines in the accidents and what falls within ageing factors (psychomotor retardation, divided attention disorder etc.);
- in addition, a majority of these studies are based on the use of administrative databases (prescriptions recorded in the pharmacy, police data, census of admissions into the emergency departments etc.) which do not reveal the actual administration of benzodiazepine on the day of the accident, the absorbed dose or the time between the administration and the accident.

Despite the methodological limits and the confounding factors, several epidemiological studies evaluating the link between the use of benzodiazepines and the occurrence of road traffic accidents appear to be in favour of an increased risk of accidents in users of benzodiazepines regardless of their age. However, the results are more contradictory in patients aged 65 years or over due to the numerous confounding factors. The impact of the dose, duration of exposure and the elimination half-life of benzodiazepines on this association is not clearly established even though the risk appears increased with the dose and reduced with the duration of exposure. Overall, the available data do not enable the benzodiazepines and benzodiazepine-like agents to be distinguished in terms of road traffic accidents.

In 2013, the FDA recommended reducing the dosages of zolpidem[35] following the results of a study revealing a reduced ability to drive a vehicle with blood levels of zolpidem of around 50 ng/ml whilst a pharmacokinetic study conducted in 250 men and 250 women revealed that 15% of women and 3% of men had concentrations of zolpidem over 50 ng/ml around 8 hours after taking a 10 mg dose of the immediate release formulation.
In Europe, in March 2014, the EMA recommended changes to the SPC and package leaflet of medicinal products containing zolpidem following reports of adverse effects including

[32] Johansson K et al. Traffic dangerous drugs are often found in fatally injured older male drivers. J Am Geriatr Soc 1997; 45: 1029-31.
[33] Orriols L et al. Prescription medicines and the risk of road traffic crashes: results of a French registry-based study. PLoS Med 2010; 7.
[34] Orriols L et al. Benzodiazepine-like hypnotics and the related risk of road traffic accidents. Clin PharmTher 2011; 89: 595-601.
[35] FDA [Food and Drug Administration]. Drug safety communications. Risk of next morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). Janvier 2013.
http://www.fda.gov/downloads/Drugs/DrugSafety/UCM335007.pdf

somnambulism states and road traffic accidents.[36,37] At this time, the ANSM issued a reminder that a duration of 7 to 8 hours must be respected before undertaking any activity which requires alertness and that benzodiazepine hypnotics and benzodiazepine-like agents must not be used to treat awakenings in the middle of the night.[38]
In France, a pictogram indicating the risk level (3-level classification) is affixed to the external packaging of medicinal products likely to "impair the ability to drive a vehicle". All medicinal products from the benzodiazepine class fall within the highest risk levels of this classification (level 3 for hypnotics and level 2 for anxiolytics).

4.2.3 Altered cognitive impairment and dementia

a) Short-term effects

The short-term cognitive effects (impaired alertness, memory disorder, confusion, disorientation) are well-known adverse effects of benzodiazepines and benzodiazepine-like agents.[1,39]
Anterograde amnesia, which can occur at therapeutic doses and the risk of which increases proportionally with the dose, is a common adverse effect (≥1/100, <1/10) in the SPC.

b) Long-term effects

Their long-term effects on cognitive functions and dementia occurrence remain subjects of debate.

In January 2012, the "PGR-PEPI" [Risk Management plan – pharmacoepidemiology] group[40] of ANSM carried out a review of epidemiological studies that evaluated the association between exposure to benzodiazepines and the cognitive impairment or the occurrence of dementia.[2] Ten published epidemiological studies were analysed. Their results are contradictory:
- Five studies reported a positive association between taking benzodiazepine and the occurrence of cognitive disorders or dementia;[41,42,43,44,45]
- Four studies did not reveal any association;[46,47,48,49]

[36] EMA [European Medicines Agency]. Review of zolpidem-containing medicines started. July 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Zolpidem-containing_medicinal_products/Procedure_started/WC500145745.pdf
[37] EMA [European Medicines Agency]. PRAC recommends product information of zolpidem be updated with new advice to minimise the risk of next-morning impaired driving ability and mental alertness. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Zolpidem-containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500162553.pdf
[38] ANSM [National Medicines and Health Products Safety Agency] Médicaments contenant du zolpidem – Point d'information. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Medicaments-contenant-de-la-domperidone-du-zolpidem-ou-de-l-hydroxyzine-retour-sur-la-reunion-d-avril-2014-du-CMDh-Point-d-Information
[39] Curran HV et al. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. Psychol Med 2003; 33: 1223-37.
[40] PGR-PEPI group: risk management plan - pharmacoepidemiological studies group.
[41] Wu CS et al. Effect of Benzodiazepine Discontinuation on Dementia Risk. Am J Geriatr Psychiatry 2010.
[42] Wu CS et al. The association between dementia and longterm use of benzodiazepine in the elderly: nested case-control study using claims data. Am J Psychiatry 2009; 17: 614-20.
[43] Lagnaoui R et al. Benzodiazepine use and risk of dementia: a nested case-control study. J Clin Epidemiol 2002; 55: 314-8.
[44] Paterniti S et al. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. J Clin Psychopharmacol 2002; 22: 285-93.
[45] Gallacher J, Elwood P, Pickering J, et al. Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). J Epidemiol Community Health. 2012 Oct; 66(10): 869-73.
[46] Lagnaoui R, Tournier M, Moride Y, Wolfson C, Ducruet T, Begaud B, et al. The risk of cognitive impairment in older community-dwelling women after benzodiazepine use. Age Ageing 2009; 38: 226-8.

- One study revealed a protective association between taking benzodiazepines and altered cognitivefunctions.[50]

Two other studies have been published since January 2012:
- the study by Billioti de Gage *et al.*[51] ("Benzodem" study):

This study evaluated the association between the use of benzodiazepines or benzodiazepine-like agents and dementia occurrence from the French PAQUID cohort.[52] In total, 1063 men and women not presenting dementia were included. After 15 years of follow-up, 253 cases of dementia were diagnosed. The risk of dementia was higher in patients newly exposed to a benzodiazepine or benzodiazepine-like agent in relation to non-exposed patients (HR = 1.60; 95% CI [1.08 to 2.38]). A sensitivity analysis considering the presence of depressive symptoms confirmed this association (HR = 1.62; 95% CI [1.08 to 2.43]).
A secondary analysis including patients newly exposed to a benzodiazepine or benzodiazepine-like agent at different times during the follow-up in the cohort also revealed an increased risk of dementia in newly exposed patients in relation to non-exposed patients (HR = 1.40; 95% CI [1.06 to 1.85]).
Finally, in an additional case-control study, the patients exposed to a benzodiazepine or benzodiazepine-like agent also had an increased risk of dementia in relation to non-exposed subjects (adjusted OR = 1.55; 95% CI [1.24 to 1.95]). The risk of dementia was increased in chronic users (> 9 years) but not in more recent users (3 to 5 years).

- Mura *et al.* study:[53]

This study evaluated the impact of long-term use of benzodiazepines or benzodiazepine-like agents on cognitive performances using data from the French "Three Cities" cohort. In total, 969 people who reported taking benzodiazepine or a benzodiazepine-like agent for 2, 4 or 7 consecutive years and 4226 non-exposed people were included. Analyses were based on the scores from several neuropsychological tests and enabled a latent cognitive process common to all tests to be modelled. This study revealed the existence of an association between the chronic use of benzodiazepines or benzodiazepine-like agents and a reduced cognitive level for the majority of the neuropsychological tests used. However, no association was found between the chronic use of benzodiazepines and an accelerated cognitive decline.

The epidemiological studies that evaluated the association between taking benzodiazepines and cognitive impairment or the occurrence of dementia have very heterogeneous methodology (enrolled population, definition and evaluation of cognitive disorders or dementia, study methodology [cohort or case control], measure of benzodiazepine exposure etc.). Their results are difficult to compare.
The discordance of the results also reflects the methodological limits of the studies; the main limits have been revealed by the PGR-PEPI group:
- the protopathic bias which corresponds to the difficulties ensuring that the patients included in the studies were not presenting the first symptoms of dementia before initiation of treatment with benzodiazepines;

[47] Allard J, Artero S, Ritchie K. Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance. Int J Geriatr Psychiatry 2003; 18: 874-8.
[48] Hanlon JT, Horner RD, Schmader KE, Fillenbaum GG, Lewis IK, Wall WE, Jr., et al. Benzodiazepine use and cognitive function among community-dwelling elderly. Clin Pharmacol Ther 1998; 64: 684-92.
[49] Dealberto MJ, McAvay GJ, Seeman T, Berkman L. Psychotropic drug use and cognitive decline among older men and women. Int J Geriatr Psychiatry 1997; 12: 567-74.
[50] Fastbom J, Forsell Y, Winblad B. Benzodiazepines may have protective effects against Alzheimer disease. Alzheimer Dis Assoc Disord 1998; 12: 14-7.
[51] Billioti de Gage S et al. Benzodiazepine use and risk of dementia: prospective population based study. BMJ. 2012. 345.
[52] Cohort of 3777 patients aged 65 years or over between 1987 and 1989 living in Gironde and Dordogne.
[53] Mura T et al. Chronic use of benzodiazepines and latent cognitive decline in the elderly: results from the Three-city study.Eur Neuropsychopharmacol. 2013; 23: 212-23.

- depletion of susceptible bias, corresponds to the loss of high-risk patients during follow-up after they have presented the studied event;
- the lack of information on the actual duration of exposure to benzodiazepines (dose, dosage, treatment duration and cumulative dose) which could be at the origin of a misclassification;
- exclusion of numerous subjects from the initial cohorts could be at the origin of selection bias if the reason for exclusion was linked to dementia (e.g.: inclusion only of subjects able to answer the questions) or misclassification bias (e.g.: inclusion only of subjects for whom the information of benzodiazepine use is available);
- the differences in data collection method between the studies;
- the lack of representativeness of some samples and the impossibility to extrapolate results;
- the fact that certain potential confusion factors were not properly taken into account;
- the methods of taking into account the effect of age on the occurrence of dementia.

Given these limits, the available data do not support a conclusion on whether or not there is a causal association between taking benzodiazepines and the onset of dementia.

05 INFORMATION ACTIVITIES ON PROPER USE

The main information activities intended for healthcare professionals and the general public carried out or being carried out by HAS are covered here.

Themes	Actions taken or ongoing
Information for the general public	- "Being senior and sleeping better" (Être senior et mieux dormir) brochure (including lifestyle and diet advice) intended for elderly patients (2013)[54] - "Being senior and sleeping better" poster for medical practices and for dispensing pharmacies (2013)[55] - "Patient, Physician and Pharmacist Testimonials" (Témoignage Patient, Médecins, Pharmaciens) video available on the HAS website, facebook and youtube (2013)[56]
Information for prescribers	- "Being senior and sleeping better" programme for improved practices (updated in 2013) - PsychoSA (improved prescribing of psychotropic medicinal products in elderly patients) programme for improved practices (since 2007) - Good practice recommendations for the methods of discontinuing benzodiazepines in elderly patients and tools to help the physician in practice (2007)[5] - Good practice recommendations on the management of adult patients complaining of insomnia in general medicine and tools to help the physician in practice (2006)[3]
Information for pharmacists	- Actions sheet for practice improvement intended for community pharmacists on "Sleeping tablets and sleep in the elderly patient" (2013)[57]

[54] http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-03/echange_patient_quelques_conseils_pour_mieux_dormir_vf.pdf.
[55] http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-09/affiche_a4_somniferes.pdf
[56] http://www.has-sante.fr/portail/jcms/c_1312411/fr/videos-troubles-du-sommeil-stop-a-la-prescription-systematique-de-somniferes-chez-les-personnes-agees.
[57] http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-03/fiche_action_sommeil_somniferes_et_sujet_age_vf.pdf.

06 USAGE DATA

06.1 France

6.1.1 GERS [Group for the preparation and implementation of statistics] sales data

According to the GERS sales data, 48.8 million boxes of benzodiazepine hypnotics and benzodiazepine-like agents were sold in dispensing pharmacies in 2013. Zopiclone and zolpidem represent 81% of sales (see Table 4).

Table 4. Number of boxes sold in dispensing pharmacies in 2013 (GERS data).

INN	Proprietary medicinal product	Number of boxes sold
zolpidem	STILNOX	23,308,024
zopiclone	IMOVANE	16,409,570
lormetazepam	NOCTAMIDE	6,162,473
loprazolam	HAVLANE	1,822,988
nitrazepam	MOGADON	425,267
estazolam	NUCTALON	453,062
flunitrazepam	ROHYPNOL	266,317
Total		**48,847,701**

6.1.2 REFUND INFORMATION

The EGB [General sample of beneficiaries] is a permanent sample representing 1/97th of insured people registered with French national health insurance, Agricultural Social Mutual Fund, and Independants Fund. It contains anonymous information on the general characteristics of patients, their use of refunded non-hospital treatments and hospitalisations (PMSI - MCO) [programme for clinical information systems - medicine, surgery and obstetrics].
According to the analysis of EGB refund data during 2013, 36,854 patients had at least one refund for a benzodiazepine hypnotic or benzodiazepine-like agent in 2013.
Extrapolation of these data to the French population[58] produces an estimation of between 3.9 and 4 million people exposed in France in 2013.

Table 5. Refunds for benzodiazepine hypnotics or benzodiazepine-like agents in 2013 (EGB)

INN	Proprietary medicinal product	EGB number	number extrapolated to the French population	95 % CI Lower limit	95 % CI Upper limit
zolpidem	STILNOX	20,829	2,240,943	2,211,034	2,270,851
zopiclone	IMOVANE	13,777	1,482,235	1,457,765	1,506,704
lormetazepam	NOCTAMIDE	4122	443,476	429,983	456,969
nitrazepam	MOGADON	418	44,972	40,662	49,281
loprazolam	HAVLANE	367	39,485	35,446	43,523
estazolam	NUCTALON	97	10,436	8359	12,513
flunitrazepam	ROHYPNOL	20,829	2,240,943	2,211,034	2,270,851
Total*		**39,041**	**3,965,034**	**3,925,796**	**4,004,272**

* the same person may have received refunds for several benzodiazepine hypnotics or benzodiazepine-like agents.

[58] The EGB data was extrapolated to the French population by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries present in the EGB on 01/01/2013 (n = 609,159) in proportion to the French population on 01/01/2013 (n = 65,542,916). The extrapolation coefficient obtained is 1/107.6.

6.1.3 Analysis of the exposed population and treatment modalities by ANSM[6]

Using EGB data, ANSM analysed the treatment modalities of patients exposed to a benzodiazepine. Only the results concerning benzodiazepine hypnotics or benzodiazepine-like agents are shown here.
In patients who received their first refund in 2012 (n = 33,877):

- in 80% of cases, the benzodiazepine hypnotic was prescribed by a general practitioner;
- the median age of patients was 58 years; one in three patients was aged 65 years or over and almost 12% of patients were aged 80 years or over;
- 59% (n=19,944) of patients were dispensed the medicinal products at least three consecutive times during the year and had a median exposure of 4 months during the year.

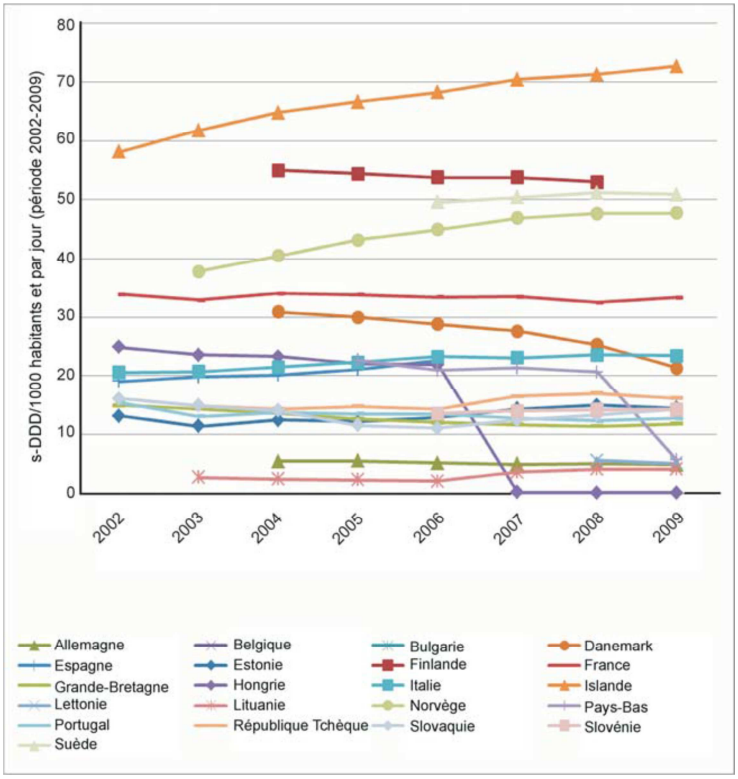
In patients who received their first refund between 2007 and 2012 (n = 93,795):

- 50% (n=46,928) of patients only had the medicinal product dispensed once throughout the study period;
- almost 17% of patients were treated without interruption with a median exposure time of 4.9 years.

06.2 Europe

In 2009, France was in 5th position for the use of hypnotics, behind the Northern European countries (Iceland, Finland, Norway, Sweden).[59]

Figure 1. Change in the level of use of hypnotics (ATC classification N05C) in different European countries including France from 2002-2009.[59]



[59] Expertise collective Inserm. Médicaments psychotropes : consommations et pharmacodépendances Paris 2012.

07 SUMMARY AND DISCUSSION

The efficacy of benzodiazepine hypnotics and benzodiazepine-like agents (zolpidem and zopiclone) has been demonstrated in relation to placebo in the treatment of insomnia mainly in subjective sleep evaluations. The quantity of effect is low, around one extra hour of sleep per night.
The efficacy of benzodiazepines and benzodiazepine-like agents has mainly been evaluated over short periods (between one night and 6 weeks). The maintenance of efficacy over a longer term has not been demonstrated.
The data do not support a conclusion of an efficacy difference between the compounds. The studies which compared benzodiazepine hypnotics or benzodiazepine-like agents with each other are mostly old and of low methodological quality.

The main adverse effects associated with the use of benzodiazepines and benzodiazepine-like agents are memory disorders, reduced alertness or drowsiness, behavioural disorders and an increased risk of falls particularly in elderly patients. Even though short-term alteration of cognitive performance is recognised, the current data do not support a conclusion on whether or not there is an association between taking benzodiazepines and the onset of dementia.
Prolonged exposure to benzodiazepines and benzodiazepine-like agents results in a risk of pharmacological tolerance and a risk of psychological and physical dependence.
The data do not support a conclusion on whether or not there is a difference in adverse effect onsets depending on the pharmacokinetic characteristics of the products.

According to an Inserm analysis, France is in 5th position for the use of hypnotics, behind the Northern European countries (Iceland, Finland, Norway, Sweden).
In 2013, 48.8 million boxes of benzodiazepine hypnotics and benzodiazepine-like agents were sold in dispensing pharmacies. Zopiclone and zolpidem represent 81% of sales. In an analysis performed on a general sample of beneficiaries of health insurance (EGB), amongst the patients newly exposed to a benzodiazepine hypnotic or a benzodiazepine-like agent between 2007 and 2012, 50% were dispensed the product once over the study period; over this same period, 17% of patients were treated continuously with a median exposure duration of around 5 years.

The Ministry of Health, HAS and ANSM are engaged in a concerted action plan aimed at limiting the use of benzodiazepines and promoting their proper use. Several information activities intended for healthcare professionals and patients were carried out by HAS in 2013. Regulatory measures are also being discussed (mandatory security prescriptions for benzodiazepines, reduced packaging etc.).

08 THERAPEUTIC USE

This summary has been prepared from recommendations on the management of insomnia in general medicine and recommendations on methods to discontinue hypnotics.[3,5]

The initiation of treatment for insomnia justifies a consultation dedicated to this subject.

In all cases of insomnia, it must be ensured that the sleep habit and the sleep-wake cycle balance rules are followed (see box below). These rules can sometimes be sufficient to restore sleep in cases of mild insomnia without comorbidities.

Sleep habit rules

- Sleep as needed but no more; avoid long naps (> 1 hour) or napping too late in the day (after 16:00);
- Adopt a regular schedule of waking up and going to bed. For older people, go to bed later;
- Limit noise, light and excessive temperature in the bedroom;
- Avoid caffeine, alcohol and nicotine;
- Exercise during the day, but generally not after 17:00;
- Avoid meals which are too heavy in the evening.

In the case of difficulty falling asleep:
- Mark the moment of waking up (shower, exercise, brightly lit environment);
- Avoid bright light and exercise in the evening.

In the case of waking up too early:
- Do not stay in bed after waking up;
- In the evening, exercise and maintain brightly lit environment.

Cognitive behavioural therapies (CBT) can be suggested as a first-line treatment with all forms of insomnia other than occasional.
These techniques include different methods: sleep restriction, stimulus control, relaxation techniques, and actual cognitive therapy.
They have demonstrated short-term efficacy on sleep onset latency and the number of awakenings during the night, particularly the stimulus control method.
In France, they are underdeveloped and not covered by health insurance.

08.1 Prescription of a benzodiazepine hypnotic

The prescription of a benzodiazepine hypnotic or benzodiazepine-like agent must only be used in a short-term strategy.

The lowest individual effective dose must be sought and prescribed for a limited period from several days to a maximum of 4 weeks including the dose reduction period. The combination of several sedative medicines is contraindicated.

The choice of a hypnotic depends on:
- the profile of the patient's insomnia (sleep onset insomnia, difficulty staying asleep or waking up too early);
- the time (Tmax) and the duration of action of the product, linked to the dose used and the half-life;
- the risk of interactions with other medicinal products, in particular with other psychotropic medicines (if possible, avoid combining several psychotropic medicines);
- the patient's physiological status (age, renal and hepatic status);
- the type of activities likely to be performed by the patient after administration.

The intensity or duration of the residual effects of a product depends little on the half-life but on its nature, the dose, onset of action, frequency of administration and the age and sex of the patient, their lifestyle and associated conditions.

Whenever a benzodiazepine hypnotic or benzodiazepine-like agent is prescribed, the patient must be informed about the treatment conditions, the adverse effects and the precautions for use. In particular, the patient must be informed about the low effect of these medicinal products, the risks of memory disorders, somnolence, behavioural disorders and falls as well as tolerance and dependence phenomena. Prescription must be avoided in patients at risk of developing dependence (patients already on benzodiazepines, using high doses or with a history of other dependence, drug-related or not).

Changing from one proprietary medicinal product to another is only justified if the patient has adverse effects directly due to the product used, or possibly as part of withdrawal.

Regardless of the chosen therapy, there should be at least one additional consultation at the end of the prescription period to re-assess the situation, if only due to the risk of the disorder becoming chronic.

If the situation appears likely to last for several weeks, or even longer, non-pharmacological treatment should be suggested, in particular cognitive-behavioural type psychological treatment.

It should be remembered:
- **that no benzodiazepine hypnotic or benzodiazepine-like agent has an indication in the treatment of chronic insomnia;**
- **that dependence on these products is possible, even in the absence of dependence risk factors;**
- **that these treatments can be an insomnia maintenance factor, in particular due to the rebound insomnia which they can cause at discontinuation.**

08.2 Strategy of benzodiazepine hypnotics discontinuation

At initiation of treatment with a benzodiazepine hypnotic or benzodiazepine-like agent, the physician must explain to the patient about the duration of treatment and its discontinuation methods.

Regardless of the chosen strategy, outpatient or in hospital, with or without specialised care, discontinuation must be gradual, over a period of several weeks (normally 4 to 10 weeks) to several months, more particularly in long-term users or those receiving high doses due to the risk of withdrawal syndrome and rebound effects.

Even though the aim is complete discontinuation of the use of benzodiazepines or benzodiazepine-like agents, obtaining a reduced dosage should be considered a favourable result in itself.

There is no justification to suggest a substitute drug therapy during withdrawal. Emphasis should be placed on accompanying non-drug related measures for as long as necessary.

If the discontinuation strategy fails, the patient should be encouraged to start again at a later date after the reasons for failure have been assessed.

08.3 Specificities of insomnia management in elderly patients

Management of sleep disorders in the elderly patient must take account of various parameters:
- physiological modifications of sleep (lighter, more fragmented, more spread out over the 24 hour period);
- daytime consequences of insomnia, more marked than in middle age (psychomotor retardation);
- less effective metabolism slowing down the pharmacokinetics of medicinal products;
- greater frequency of comorbidities and treatment with multiple medications.

The general objective of insomnia management in the elderly patient should be promotion of staying awake during the day, physical or intellectual activities, going to bed late and respecting a regular sleep/wake rhythm.

Non-pharmacological treatments are preferred.

Taking benzodiazepine hypnotics or benzodiazepine-like agents exposes elderly patients in particular to falls and their consequences, as well as cognitive impairments and road traffic accidents.

Elderly patients often take benzodiazepine hypnotics for long periods. For them, treatment discontinuation may mean calling into question a certain balance or even lifestyle to which they are accustomed. Therefore, the advantages and risks associated with benzodiazepine use and its interruption should be analysed with each patient.

08.4 Errors to be avoided

- **Routinely prescribing a hypnotic without assessing the patient's situation**
- **Ignoring depression or another psychiatric disorder causing the sleep disorder**
- **Neglecting a symptom suggestive of sleep apnoea syndrome (loud snoring, daytime somnolence, headaches when waking up, excess weight)**
- **Combining several benzodiazepines, hypnotics or anxiolytics**
- **Giving a repeat prescription without re-assessing the patient's situation**
- **Sudden discontinuation of treatment with a benzodiazepine or benzodiazepine-like agent**

09 TRANSPARENCY COMMITTEE CONCLUSIONS

09.1 Re-assessment of the actual benefit

◗ Sleep disturbances and the associated daytime repercussions can have harmful effects on daily functioning and the occurrence or worsening of somatic or psychological conditions. Occasional or transient insomnia can become chronic and can therefore be a source of personal and social complications with socio-professional repercussions.

◗ The efficacy/adverse effects ratio for benzodiazepine hypnotics and benzodiazepine-like agents is low in the short-term and insufficient after 4 weeks.

◗ These proprietary medicinal products are in the symptomatic therapy category.

◗ The prescription of hypnotics should be part of a second-line short-term strategy if the sleep habit rules are not sufficient. At initiation of a treatment, the physician must explain to the patient about the treatment duration and the discontinuation modalities due to the risks linked with the treatment.

◗ Public health benefit:

Sleep disorders represent a significant public health burden given their frequency and their human, social and economic impact.[3] The observation of a high use of benzodiazepines in France without knowing the exact justification, the observation of the deleterious consequences of these medicinal products on individuals, with an impact on the community (accidents, falls, dependence, addiction, etc.) and in light of their low individual efficacy lead to the conclusion that these medicinal products have a potentially negative effect on public health.

Taking account of these points, the Committee considers that the actual benefit of benzodiazepine hypnotics and benzodiazepine-like agents (NUCTALON, HAVLANE, NOCTAMIDE, MOGADON, NORMISON, IMOVANE and generics, STILNOX and generics) is low in the treatment of "severe sleep disorders in the following cases: occasional insomnia, transient insomnia."

010 COMMITTEE RECOMMENDATIONS

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indication "Severe sleep disorders in the following cases: occasional insomnia, transient insomnia ".

The Committee recommends:
- **better information for the public about the risks of chronic use of these medicinal products and their proper use through a powerful and repeated media campaign aimed at the general public,**
- **enhancing the initial and continued training of healthcare professionals on the proper use of benzodiazepines and the methods for their discontinuation,**
- **developing the use and access to non-drug related treatments (cognitive behavioural therapy),**
- **supporting measures which could be recommended by ANSM as part of its work which may enable improved used of these products.**