HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

5 December 2012

STABLON 12.5 mg, coated tablet

B/30 (CIP code: 34009 329 339-1 4)
B/100 (CIP code: 34009 558 336-0 4)

Applicant: SERVIER

INN	tianeptine
ATC Code (2012)	N06AX14 (Other antidepressants)
Reason for the review	**Re-assessment of Actual Benefit at the request of the Transparency Committee** **Renewal of inclusion**
List(s) concerned	**B/30** **National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2) **B/100** **Hospital use** ((French Public Health Code L.5123-2)
Indication(s) concerned	**"Major depressive episodes (i.e. typical)."**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national procedure)	06/02/1987
Prescribing and dispensing conditions/special status	List I. Duration of prescription restricted to 28 days. To be prescribed written out fully on a secure prescription. Overlap prohibited except on the express instruction of the prescriber written on the prescription. A copy of the prescription to be held by the pharmacist for 3 years.

ATC Classification	2012	
	N	Central nervous system
	N06	Psychoanaleptics
	N06A	Anti-depressants
	N06AX	Other Anti-depressants
	N06AX14	Tianeptine

02 BACKGROUND

Tianeptine is an antidepressant, the exact mechanism of action of which is not known. It is clinically similar to the tricyclic antidepressants and to amineptine which was withdrawn from the French market in 1999 because of abuse and drug dependence and because of its hepatic (cholestatic injuries) and cutaneous (acne) adverse effects.[1]
STABLON has been marketed in France since 1989 for the treatment of major depressive episodes (i.e. typical).
In 2005, STABLON underwent an addiction vigilance survey which led to the addition of a warning about the risk of abuse and dependence in the SPC and patient leaflet.
In April 2011, the National Narcotics and Psychotropics Committee found persisting cases of tianeptine abuse and drug dependence and requested that the benefit/risk ratio of the substance be re-assessed.
On 2 February 2012, the National Marketing Authorisation Committee considered that the benefit/risk ratio for tianeptine remained positive but tightened the prescribing and dispensing conditions for the substance. Since 3 September 2012 STABLON has been subject to part of the narcotics regulations (secure prescription, prescription length restricted to 28 days).

In view of the new drug dependence findings, in November 2011, the Transparency Committee expressed a wish to re-assess the actual benefit of STABLON.

03 THERAPEUTIC INDICATION

“Major depressive episodes (i.e. typical).”

[1] Report of the National Pharmacovigilance Committee meeting on 24 January 2012. www.ansm.sante.fr

04 DOSAGE

“The recommended dosage is 1 tablet (12.5 mg) three times a day (morning, midday and evening) at the beginning of the main meals.
In chronic alcoholics, whether cirrhotic or not, no alteration of dosage is necessary.
In subjects aged over 70 years, and in subjects with renal insufficiency, the dosage should be restricted to 2 tablets per day.”

05 THERAPEUTIC NEED

Major depression is characterised by a depressed mood or loss of interest or pleasure in almost all activities. The level of functional deterioration associated with a major depressive episode varies, although stress and/or a decline in social or occupational life is seen even in mild cases. The most serious consequences of a major depressive episode are attempted suicide and suicide.
Antidepressants are the reference pharmacological treatment for moderate to severe major depressive episodes.
Twenty-three antidepressants are currently marketed in France.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The relevant comparators are the other antidepressants available in France for the treatment of major depressive episodes.

Table 1. Antidepressants indicated in major depressive episodes

INN	Same pharmacotherapeutic class? Yes/No	Proprietary medicinal product	Marketing Authorisation holder for the branded product	AB*
Selective serotonin reuptake inhibitors (SSRI)				
citalopram	No	SEROPRAM and generics	LUNDBECK	substantial
escitalopram	No	SEROPLEX	LUNDBECK	substantial
fluoxetine	No	PROZAC and generics	LILLY	substantial
fluvoxamine	No	FLOXIFRAL and generics	ABBOTT	substantial
paroxetine	No	DEROXAT and generics, DIVARIUS	GLAXOSMITHKLINE	substantial
sertraline	No	ZOLOFT and generics	PFIZER	substantial
Serotonin and noradrenaline reuptake inhibitors (SNRI)				
duloxetine	No	CYMBALTA	LILLY	substantial
milnacipran	No	IXEL and generics	Pierre FABRE	substantial
venlafaxine	No	EFFEXOR and generics, EFFEXOR LP and generics	WYETH PHARMACEUTICALS	substantial
Imipramines				
clomipramine	No	ANAFRANIL and generics	DEFIANTE FARMACEUTICA SA	substantial
amoxapine	No	DEFANYL	EISAI	substantial
amitriptyline	No	ELAVIL, LAROXYL	TEOFARMA/ MERCK SHARP & DOHME CHIBRET	substantial
maprotiline	No	LUDIOMIL	AMDIPHARM	substantial
dosulepin	No	PROTHIADEM	TEOFARMA	substantial
doxepin	No	QUITAXON	NEPALM	substantial
trimipramine	No	SURMONTIL	SANOFI AVENTIS	substantial
imipramine	No	TOFRANIL	AMDIPHARM	substantial
“Other” antidepressants				
agomelatine	No	VALDOXAN	SERVIER	substantial
mianserin	No	Generics of ATHYMIL†	--	substantial
mirtazapine	No	NORSET and generics	SCHERING PLOUGH	substantial
Selective MAOI A				
moclobemide	No	MOCLAMINE	BIOCODEX	substantial
Non-selective MAOI				
iproniazid	No	MARSILID	ALKOPHARMA	substantial

* in the treatment of major depressive episodes

† ATHYMIL ceased to be marketed in 2011

07 INTERNATIONAL INFORMATION ON MEDICINAL PRODUCT

STABLON is marketed in 15 European Union countries (France, Luxembourg, Portugal, Bulgaria, Romania, Slovakia, Poland, Malta, Hungary, Lithuania, Slovenia, Czech Republic, Austria, Latvia, Estonia) and in 66 countries throughout the World.[2]

08 SUMMARY OF PREVIOUS ASSESSMENTS

STABLON has been included on the list of proprietary medicinal products refundable by National Health Insurance and approved for use by hospitals and various public services since 16 April 1988. The conclusions of opinions given by the Transparency Committee on STABLON since it was first registered are summarized below:

Opinion of the Transparency Committee on 15 May 1991

Renewal of inclusion on the list of medicines refundable by National Health Insurance: "The Transparency Committee recommends continued inclusion for all of the indications in the Marketing Authorisation."

Opinion of the Transparency Committee on 08 March 1995

Renewal of inclusion on the list of medicines refundable by National Health Insurance: "The Transparency Committee recommends continued inclusion for all of the indications in the Marketing Authorisation."

Opinion of the Transparency Committee on 25 March 1998

Renewal of inclusion on the list of medicines refundable by National Health Insurance: "The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance."

Opinion of the Transparency Committee on 19 November 1999

Re-assessment of actual clinical benefit:
"Usual severity of the disorder treated:
The disorder treated with this proprietary medicinal product is characterised by progression to disability and/or major deterioration in quality of life.

Efficacy/Safety of use of the proprietary medicinal product:
This proprietary medicinal product is intended as symptomatic treatment.
The efficacy of this proprietary medicinal product in this indication is moderate.

Place in the therapeutic strategy
This proprietary medicinal product is a first-line therapy.
There are pharmaceutical or non-pharmaceutical alternatives to this proprietary product.

Public health benefit:

[2] Countries outside of the European Union: Togo, Madagascar, Gabon, Ivory Coast, Guatemala, Benin, Congo, Curaçao, Jamaica, Costa Rica, Trinidad and Tobago, Bahrain, Honduras, Panama, Morocco, El Salvador, Qatar, Tunisia, India, Pakistan, Venezuela, Guinea, Dominican Republic, Belarus, Turkey, Kazakhstan, Nicaragua, Kuwait, Mauritius, Argentina, Azerbaijan, Myanmar, Vietnam, Thailand, Cuba, Croatia, Brazil, Indonesia, Korea (Republic of), Guyana, Cameroon, Senegal, Egypt, Oman, Singapore, Malaysia, Yemen, Serbia, Hong Kong, Brunei Darussalam

This proprietary medicinal product has a public health benefit in view of the frequency, severity and cost of the disorder for which it is intended.
Transparency Committee conclusion
Level of actual benefit for this proprietary medicinal product: substantial.

Opinion of the Transparency Committee on 7 February 2001

Renewal of inclusion on the list of medicines refundable by National Health Insurance: "The disorder treated by this proprietary medicinal product is characterised by progression towards disability and/or a major deterioration in quality of life.

This proprietary medicinal product is intended as symptomatic treatment.

The efficacy/adverse effects ratio of this proprietary medicinal product is average.
This proprietary medicinal product is a first-line therapy.
There are pharmaceutical or non-pharmaceutical alternatives to this proprietary product.
The level of actual benefit of this proprietary medicinal product is substantial."

Opinion of the Transparency Committee on 19 July 2006

Renewal of inclusion on the list of medicines refundable by National Health Insurance:
"The data submitted by the company are not likely to change the AB from that stated in the previous Transparency Committee opinion.

Scientific data acquired about the diseases in question and their management have been incorporated. These data are not likely to change the AB from that stated in the previous Transparency Committee opinion.

The AB of this proprietary medicinal product remains substantial in this indication
The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indication and at the dosage in the Marketing Authorisation."

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

No new efficacy studies have been submitted to the Transparency Committee since the renewal of inclusion in 2006.
The available data on the efficacy of tianeptine in the treatment of major depressive episodes are summarised here.
The study references are provided in the appendix.

9.1.1 Placebo-controlled studies

a) Short-term efficacy

The short-term efficacy of tianeptine was assessed versus placebo in three double-blind, randomised studies

- the study by Cassano *et al.* (1996) (187 patients) compared tianeptine at a flexible dosage of 25-50 mg/d with placebo in patients between 18 and 60 years old with a major depressive episode (isolated or recurrent) or a bipolar disorder with a depressive episode (DSM-III-R criteria) and a MADRS score at inclusion of ≥ 25.[3] The study also contained a group treated with imipramine 100-200 mg/d. Tianeptine was superior to placebo in reducing depressive symptoms on the MADRS scale at 6 weeks (final MADRS score 17.3±1.6 for tianeptine compared with 22.3±1.5 for placebo, p = 0.012). A higher percentage of patients responded (fall in MADRS score ≥ 50%) in the tianeptine group than in the placebo group (56% for tianeptine compared with 32% for the placebo, p = 0.030). No statistical difference in efficacy was seen between tianeptine and imipramine;
- the study by Costa E Silva *et al.* (1997) (126 patients) compared tianeptine at flexible doses of 25-50 mg/d with placebo in patients between 18 and 60 years old with a major depressive episode (isolated or recurrent) or bipolar disorder with a depressive episode (DSM-III-R criteria) and a MADRS score at inclusion of ≥ 25. Tianeptine was superior to placebo on the MADRS score at 6 weeks (final score of 16.3±11.5 compared with 22.0±13.8, p = 0.007). No difference was seen between tianeptine and placebo in the percentage of responders (58% compared with 41%, p = 0.086);
- the Montgomery study (1997) [unpublished] (244 patients) compared tianeptine at doses of 37.5 and 75 mg/d with placebo in patients between 18 and 65 years old with a major depressive episode (isolated or recurrent) (DSM-III-R criteria) and a MADRS score at inclusion of ≥ 24. This study showed no difference in efficacy between the two active groups and placebo on the MADRS score or percentage responder rate.

b) Efficacy in preventing recurrences of depression

The study by Dalery *et al.* (1997 & 2001) compared the efficacy of tianeptine 37.5 mg/d with placebo in preventing relapses (during the first 6 months of treatment) and recurrences of depression (after 6 months) in patients who responded to tianeptine treatment.
Two hundred and sixty-eight hospitalised and ambulatory patients suffering from a recurrent major depressive episode (Hamilton Depression Rating Scale [HDRS] 21 item score ≥ 17 and at least one depressive episode during the previous 5 years) were given tianeptine for 6 weeks.
After 6 weeks, 185 responder patients were included in the double-blind, randomised phase of the study to be given tianeptine 37.5 mg/day (n = 111) or placebo (n = 74).
At 18 months, the percentage relapse and recurrence rate (clinical global impression [CGI]

[3] The MADRS scale (Montgomery and Asberg Depression Rating Scale) assesses the severity of depressive symptoms; it contains 10 items scored from 0 to 6 (maximum score = 60).

score ≥ 4 and/or HDRS score ≥ 15) was lower in the tianeptine group than in the placebo group (p = 0.002): 18 relapses or recurrences in the tianeptine group (16%) compared with 27 in the placebo group (36%).

9.1.2 Studies versus an active comparator

a) Studies versus selective serotonin reuptake inhibitors (SSRIs)

A total of eight double-blind, randomised studies have compared the efficacy of tianeptine with an SSRI: fluoxetine (three studies: Alby *et al.* 1993a; Lôo *et al.* 1999 & 2001; Novotny & Faltus 2002), paroxetine (three studies: Lépine *et al.* 2001b; Waintraub *et al.* 2002; Nickel *et al.* 2003), sertraline (two studies: Szadoczky & Füredy 2002; Kasper 2003 [unpublished]). Depending on the study the patients included had a diagnosis of major depressive episode or dysthymia, a depressive episode as part of bipolar disorder and in one study, a major depressive episode associated with generalised anxiety disorder. The diagnostic criteria were those from the DSM-III-R, ICD-10 or DSM-IV). The study follow-up period lasted from 6 weeks to 3 months. In seven studies, the primary efficacy endpoints were depressive symptoms on the Hamilton depression scale or the MADRS scale. In the study by Nickel *et al.* (2003), the main analysis compared the neurobiological effects of tianeptine to paroxetine. Clinical efficacy was a secondary endpoint.
These studies showed no difference in efficacy between tianeptine and the comparator SSRIs.
None of these studies contained a placebo group which would allow their internal validity to be tested.

Meta-analysis by Kasper *et al.* (2002)
A meta-analysis of five of these studies was performed (1348 patients).[4] Tianeptine 37.5 mg/day was compared with fluoxetine (two studies), paroxetine (two studies) and sertraline. The endpoints were the total scores on the MADRS scale, the scores for items 1, 2 and 3 on the clinical global impression scale and the percentage of responders (fall in MADRS score ≥ 50%) at 6 weeks.
No difference was seen in efficacy between tianeptine and the comparator SSRIs on MADRS score, percentage responder rate or clinical global impression after treatment for 6 weeks.

b) Studies versus tricyclic antidepressants

Six double-blind, randomised studies have compared the efficacy of tianeptine to a tricyclic antidepressant: imipramine (two studies: Cassano *et al.* 1996; Ostaptzeff 1981), amitriptyline (four studies: Invernizzi *et al.* 1994; Guelfi 1996 [unpublished]; Guelfi *et al.* 1989; Lôo *et al.* 1988 in a population withdrawing from alcohol). Depending on the study, the patients included had a major depressive episode, a major depressive episode as part of bipolar disorder or anxiety-depression disorder. The maximum study follow-up period was 8 weeks.
No difference in efficacy was seen between tianeptine and the tricyclic comparator in five studies. In the study by Guelfi 1996 [unpublished] realised in 288 patients with anxiety-depression disorder and MADRS score ≥ 20, amitriptyline was more effective than tianeptine (final MADRS score: 11.6±6.4 for amitriptyline compared with 14.2±11.1 for tianeptine, p = 0.024).
With the exception of the study by Cassano *et al.* 1996, none of these studies contained a placebo group.

[4] The study by Alby et al. 1981 was excluded because the population was too heterogeneous, including patients with mood disorders, and the Kasper et al. 2003 and Nickel et al. 2003 studies were not available at the time of the meta-analysis.

c) Studies against other antidepressants

Two studies compared tianeptine to mianserin:

- one study in 315 elderly patients (70 years of age or older) suffering from a major depressive episode according to DSM-III-R criteria (this study is presented in the next paragraph) (Brion *et al.* 1996);
- a study in 152 patients suffering from adaptation disorder (Ansseau *et al.* 1996).

One study compared tianeptine with maprotiline in 83 premenopausal or menopausal women suffering from anxiety and depression symptoms (Chaby *et al.* 1993), one study compared tianeptine with viloxazine in 40 patients suffering from Parkinson's Disease or neurovascular disease (Buge 1981 [unpublished]) and one study compared tianeptine with nomifensine in 40 patients suffering from depression (Weiss *et al.* 1981).

9.1.3 Studies in specific populations

a) Elderly

The efficacy of tianeptine in the elderly has been assessed in four studies:

- one study against mianserin in 315 patients aged 70 or older with a diagnosis of a major depressive episode according to DSM-III-R criteria (Brion *et al.* 1996);
- two non-comparative studies which assessed the medium-term effect of tianeptine (one study lasting 3 months and one study lasting 1 year) in elderly people with a diagnosis of depression or mood disorder (Saiz-Ruiz *et al.* 1998, Chapuy *et al.* 1991);
- one study which compared tianeptine with viloxazine (Marketing Authorisation rescinded) in the treatment of depressive symptoms in 40 patients between 41 and 78 years old suffering from Parkinson's Disease or neurovascular disease (Buge study 1981 [unpublished]).

<u>Tianeptine versus mianserin in an elderly population suffering from depression or dysthymia</u> (Brion *et al.* 1996)

Tianeptine was compared with mianserin in a double-blind, randomised, 6-month study in 315 patients aged 70 years or older (average age 78.5 years) with a diagnosis of a major depressive episode according to DSM-III-R criteria, a MADRS score of ≥ 24 and a HARS score of ≥ 18.

The patients were randomised into three groups: tianeptine 25 mg/d, tianeptine 37.5 mg/d or mianserin 30 mg/d. The main efficacy endpoints were the final symptom score on the MADRS scale (primary endpoint) and Hamilton anxiety scale, quality of life and clinical impression scored by the patients and investigators.

No difference in efficacy was seen between the three groups. The final MADRS scores were 13.9 in the tianeptine 25 mg group, 12.7 in the tianeptine 37.5 mg group and 14.3 in the mianserin group. The improvement rates on the MADRS scale were 53% in the tianeptine 25 mg group, 56% in the tianeptine 37.5 mg group and 50% in the mianserin group.

b) Population suffering from alcoholism or drug addiction.

The efficacy of tianeptine in a population suffering from depressive disorder after alcohol withdrawal was assessed principally in three studies:

- one double-blind, randomised study versus amitriptyline in 129 patients suffering from depressive disorders following alcohol withdrawal (Lôo *et al.* 1988);
- one double-blind randomised study versus ATRIUM (phenobarbital /febarbamate/difebarbamate - Marketing Authorisation suspended) in 37 patients suffering from depressive disorders following alcohol withdrawal (Grivois *et al.* 1981);
- one non-comparative study which assessed the one-year effect of tianeptine in 130 patients suffering from depressive disorders following alcohol withdrawal (Malka *et al.* 1992).

The efficacy of tianeptine has also been assessed in a non-comparative study in 30 patients withdrawing from opiates (Lôo *et al.* 1987).

Tianeptine versus amitriptyline in patients suffering from depressive disorders following alcohol withdrawal (Lôo *et al.* 1988)

Tianeptine was compared with amitriptyline in a double-blind, randomised study in 129 patients suffering from a major depressive episode or mood disorders (DSM-III criteria) following alcohol withdrawal. The patients were included after 2 to 5 weeks of alcohol withdrawal. They were given tianeptine 37.5 mg/d (n = 64) or amitriptyline (n = 65) for 4 or 8 weeks. No differences were seen at 4 weeks between tianeptine and amitriptyline in the fall in MADRS depression scale scores (57% compared with 52%), percentage responders (78% compared with 64%) and fall in scores on the Hamilton anxiety scale (50% compared with 48%).

09.2 Safety/Adverse effects

9.2.1 Adverse effects quoted in the SPC of 05/11/2012

The SPC refers to the following adverse effects without estimating incidence:

"Metabolic and nutritional disorders
Anorexia, hyponatraemia

Psychiatric disorders
Nightmares, confusion, hallucinations.
Drug abuse, dependence, particularly in subjects under 50 years of age with a history of drug dependence or alcohol dependence.
Cases of suicidal thoughts or behaviour have been reported during STABLON treatment or shortly after its discontinuation (…).

Nervous system disorders
Insomnia, drowsiness, dizziness, headaches, faintness, tremor, extrapyramidal symptoms, involuntary movements.

Cardiac disorders
Tachycardia, extrasystoles, precordial pain.

Vascular disorders
Hot flushing

Respiratory, thoracic and mediastinal disorders
Respiratory discomfort

Gastro-intestinal disorders
Gastralgia, abdominal pain, dry mouth, nausea, vomiting, constipation, flatulence.

Skin and subcutaneous tissue disorders
Maculopapular or erythematous rash, pruritus, urticaria, acne, very occasional bullous reactions.

Musculoskeletal and systemic disorders
Myalgia, lumbar pain.

Hepatobiliary disorders
Increased liver enzymes, hepatitis that can, in exceptional cases, be severe.

General disorders and administration site abnormalities.
Asthenia, lump in throat."

9.2.2 Re-assessment by the National Pharmacovigilance Committee

In January 2012, the National Pharmacovigilance Committee (CNPV) re-assessed the safety profile of tianeptine.[1]
Based on the spontaneous notifications obtained in France between first marketing in 1989 and September 2011, 426 serious and 501 non-serious cases were reported.
The most frequently reported serious adverse effects were hepatobiliary (increased transaminases, hepatitis), neurological (seizures, drowsiness, tremor, involuntary movements, extrapyramidal symptoms), psychiatric (confusion, hallucinations), cutaneous (erythema, bullous eruptions), haematological (thrombocytopenia, agranulocytosis), cardiac (hypotension, tachycardia) and metabolic (hyponatraemia).

The CNPV came to the following conclusion:

> "The adverse effects reported for tianeptine since it was first marketed are uncommon and of modest severity and should be considered against the high sales volume and high level of prescriptions, experience since it was first marketed and the very adverse safety profile of amineptine which was withdrawn from the market. Some members of the CNPV highlighted the fact that tianeptine, which is very widely prescribed in the elderly, appears to be generally well tolerated in this population in view of the spontaneous notification data and the clinical experience with other antidepressants. The National Committee also noted the opinion of the psychiatry working group which has assessed the efficacy of tianeptine as being "modest" based on the available studies.
>
> The CNPV considered that the majority of the pharmacovigilance data apart from the known cases of abuse and drug dependence did not in themselves justify a re-assessment of the benefit/risk balance of tianeptine (22 against, 3 abstentions, 4 for). However, it decided unanimously that the decision of the National Narcotics and Psychotropics Committee to vote for a re-assessment of the benefit/risk ratio of tianeptine based on abuse and drug dependence data was justified. It therefore supported this approach."

This pharmacovigilance assessment also revealed or confirmed several adverse effects not present in the SPC for proprietary medicinal products containing tianeptine.
Following this assessment, the following adverse effects were added to the SPC (amendment to the Marketing Authorisation of 20/08/2012):

- "increase in liver enzymes, hepatitis that can, in exceptional cases, be severe"
- "extrapyramidal symptoms and involuntary movements"
- "confusion, hallucinations"
- "hyponatraemia"
- "bullous reactions, in exceptional cases."

9.2.3 Abuse and dependence

9.2.3.1 Measures taken by Afssaps following the addiction safety survey in 2005

An addiction safety survey was carried out on STABLON in 2005 and estimated the incidence of cases of abuse and drug dependence as being between 1 and 3 per 1,000 patients treated. This survey led to several measures being introduced:

- the addition of the following warning to the STABLON SPC in January 2007: "if there is a history of drug dependence or alcohol dependence the patients must be monitored very closely in order to avoid any increase in dosage" and addition of the following wording to the list of adverse effects: "drug abuse, dependence, in particular in subjects under 50 years of age with a history of drug dependence or alcohol dependence";
- a letter being distributed in May 2007 informing healthcare professionals (prescribers and pharmacists) of the amendments made to the STABLON SPC;
- two additional studies being conducted:
  - a preclinical study to assess cross-sensitisation between tianeptine and addictive substances such as benzodiazepines, psychostimulants and glutamate antagonists in the rat;
  - a clinical pharmacodynamics study assessing the presence of a psychostimulant effect at a supratherapeutic dose of tianeptine compared with methylphenidate and placebo in healthy volunteers.

The results of these two studies were presented to the National Narcotics and Psychotropics Committee on 21 April 2011 (cf. next paragraph).

9.2.3.2 Re-assessment by the National Narcotics and Psychotropics Committee

In January 2011, Servier informed Afssaps that the Marketing Authorisation for STABLON had been withdrawn in Georgia and that tianeptine had been included on the list of psychotropic agents in Russia, Ukraine and Armenia because of its misappropriation by drug addicts (intravenous injections). In this context, the decision was taken to update the survey on the potential of tianeptine for abuse and drug dependence. The results were presented to the National Narcotics and Psychotropics Committee on 21 April 2011.[5]

The National Narcotics and Psychotropics Committee examined the following data:

- the updated information on the potential of tianeptine for abuse and dependence analysed by the Nancy CEIP;
- a presentation by Servier of the results of the pharmacological studies requested by Afssaps and a literature review on the pharmacodynamic effects of tianeptine;
- an analysis of the characteristics of patients treated with tianeptine between 2006 and 2010 from data taken from the general sample of National Insurance beneficiaries.

[5] Report of the National Narcotics and Psychotropics Committee meeting on 21 April 2011. www.ansm.sante.fr

a) An update of the survey on the potential of tianeptine for abuse and dependence over the period 2006-2010

The assessment of the potential for abuse and dependence over the period 2006-2010 was based particularly on the following data:

- cases of abuse and drug dependence reported between 2006 and 2010 to CEIP, the CRPV and Servier;
- the results of the national drug dependence surveys: OSIAP, OPPIDUM, OPEMA;
- the results of a study conducted from the National Health Insurance databases in the Provence-Alpes-Côte-d'Azur and Corsica region[6];
- cases published in the literature.

The National Narcotics and Psychotropics Committee came to the following opinion:
"The sales figures for STABLON are falling (-10% between 2006 and 2009).
The data update confirms the existence of cases of abuse, with 45 cases of abuse reported over the period 2006-2010. Fewer cases of abuse were reported in 2009 and 2010 although six cases have already been reported for the first quarter of 2011.
People who take excess amounts of STABLON are mostly under 50 years old. The group of patients who take increased doses is made up of 61.4% women. Thirty of the 45 cases reported had a past history of abuse and/or other abuse concomitant with the tianeptine.
Despite the amendment to the SPC in 2007, the profile of people who overuse tianeptine is similar to the profile described in the previous survey.
The literature review reports three published cases of abuse, all in Turkey.
The data update therefore confirms the actual risk of abuse of STABLON".

b) Results of pharmacological studies requested by Afssaps and of a literature review on the pharmacodynamic effects of tianeptine

Servier presented the results of the two studies requested by Afssaps in 2007:

- a discrimination study performed on eight rats to investigate cross-sensitisation between tianeptine and increasing doses of four substances known to have addictive potential (cocaine, diazepam, phencyclidine and d-amphetamine);
- a clinical pharmacodynamics study which assessed the existence of a psychostimulant effect at a supratherapeutic dose (75 mg) of tianeptine in 18 volunteers compared with methylphenidate and placebo.

These data were analysed by the Nancy CEIP which came to the following conclusion: "these two studies do not provide formal evidence of a psychostimulant effect of tianeptine compared with cocaine, d-amphetamine or methylphenidate although they provide evidence for effects of tianeptine which are similar to psychostimulant effects. Thus, in the preclinical study, in a certain (albeit inadequate) number of ratswhich generalize for cocaine and d-amphetamine. In the clinical study the effects of tianeptine were between those of methylphenidate and placebo."

[6] Rouby F. et al. Assessment of abuse of tianeptine from a reimbursement database using 'doctor-shopping' as an indicator. Fundam Clin Pharmacol. 2012; 26: 286-94.

c) Characteristics of patients treated with tianeptine between 2006 and 2010 from data obtained from the general sample of National Health Insurance beneficiaries (EGB)

In the EGB,[7] 9556 patients received at least one reimbursement for STABLON between 2006 and 2010. A fall in the number of patients treated with tianeptine has been seen between 2006 and 2010 (-52% in women and -42% in men).
Median patient age is 57 years old. The majority are women (69%).
Median length of exposure to tianeptine is 8.3 months.
The main prescribers of tianeptine are general practitioners (86% of prescribers are in self-employed practice). Two per cent of prescribers are psychiatrists and neurologists.
A large proportion of patients (51%) only received a single reimbursement of tianeptine during the study period.
Patients with at least 12 reimbursements over the year ("regular" users) made up 41% of the people in the cohort study. Eight per cent of these patients received an estimated average dosage of over 50 mg daily (more than 4 tablets daily) and 2.4% received an estimated daily dosage of over 75 mg (over 6 tablets daily).
Ninety-five per cent of the 4877 patients who only received a single reimbursement for STABLON had previously received a reimbursement for an antidepressant other than tianeptine. All of the 4877 patients then received a prescription for an antidepressant other than tianeptine.
Within the group of "regular users", a group consisting of 1/1000th of the patients treated was considered to be deviant users of tianeptine. These were young people (40.3 years old) with a very high estimated daily dose of tianeptine (540 mg), a short treatment period (1 month) and significant doctor and pharmacy "shopping" (attending different practitioners) (three different doctors and three different pharmacies over an average period of 1 month).

d) Conclusion of the National Narcotics and Psychotropics Committee

The update of data on the potential of tianeptine for abuse and dependence led the National Narcotics and Psychotropics Committee to support the following recommendations:[5]

- re-assessment of the benefit/risk ratio for tianeptine in light of new data on the risk of drug dependence.
- increasing the awareness of the National Health Insurance so that it introduces appropriate monitoring measures for STABLON;
- questioning the Member States of the European Union in order to establish the current state of use of STABLON and cases of abuse and dependence in Europe.

9.2.4 Re-assessment of the benefit/risk ratio for proprietary medicinal products containing tianeptine by the Marketing Authorisation Committee

On 2 February 2012, the Marketing Authorisation Committee stated that the results of clinical studies submitted by the company did not cast doubt on the efficacy of tianeptine and decided that the benefit/risk ratio for STABLON remained positive subject to the tightening and increased safety of the prescribing and dispensing conditions for STABLON.[8]

Since 3 September 2012 STABLON has been subject to part of the prescribing and dispensing conditions for narcotics:

- List I;
- Duration of prescription restricted to 28 days;
- To be prescribed written out fully on a secure prescription;

[7] The EGB is a representative sample of 1/97th of all French National Health Insurance members. It contains anonymised information about the demographic characteristics of members, the services which are refundable and LTC since 2003. The EGB data are extrapolated to the French population by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries contained in the EGB on 01/01/2011 (n = 594, 370) as a proportion of the population of France on 01/01/2011 (n = 65,001,181). The extrapolation coefficient is 1/109.36.

[8] www.ansm.fr

- Overlap prohibited except on the express instruction of the prescriber written on the prescription;
- A copy of the prescription to be held by the pharmacist for 3 years.

An information letter about these changes to prescribing and dispensing conditions was sent to prescribing doctors and pharmacists on 24 July 2012.
The impact of this measure will be assessed one year after its introduction (September 2013).

The MA committee also asked the company to conduct a clinical study in the elderly.

09.3 Usage data

According to data from the EGB extrapolated to the French population,[7] the number of subjects who have been dispensed tianeptine at least once in 2011 is estimated to be **311,352 (95% CI 299,942 to 322,762)**.
Median patient age was 66 years (minimum: 3 years old, maximum: 105 years old).
Patient distribution by age band is shown in table 1.

Table 1: Patient distribution by age band

Age (years)	Total (%)
< 40	327 (11.5)
[40-60]	782 (27.5)
[60-80]	867 (30.4)
>=80	871 (30.6)
Total	2847 (100.0)

The analysis of characteristics of patients treated with tianeptine between 2006 and 2010 from the EGB by ANSM is shown in paragraph 9.2.3.

09.4 Summary & discussion

The efficacy of tianeptine has been assessed against placebo for 6 weeks in three studies:
- tianeptine was superior to placebo on MADRS scores and the percentage of responders in the study conducted by Cassano *et al.* 1996;
- tianeptine was superior to placebo on the MADRS scores but no difference was seen in the responder rate in the study by Costa E Silva *et al.* 1997;
- doses of 37.5 mg and 75 mg of tianeptine were no different to placebo in the study conducted by Montgomery in 1997.

A study on tianeptine responders showed tianeptine to be superior to placebo in reducing recurrences and relapses of depression at 18 months.
The 18 studies which compared tianeptine to other antidepressants (tricyclics, SSRIs and mianserin) did not show a difference in efficacy between tianeptine and these antidepressants. Except for one study, however, (Cassano *et al.* 1996), these studies did not contain a placebo arm allowing their internal validity to be tested.
Efficacy data in the elderly are based mostly on one study which showed no difference in efficacy between tianeptine and mianserin in people aged 70 years or older. One study in patients suffering from depressive disorders after alcohol withdrawal showed no difference in efficacy between tianeptine and amitriptyline.

Since STABLON was marketed in 1989, the most commonly reported serious adverse effects in spontaneous notifications have been hepatobiliary (increased transaminases, hepatitis), neurological (seizures, drowsiness, tremor, involuntary movements, extra-pyramidal symptoms), psychiatric (confusion, hallucinations), cutaneous (erythema, bullous eruptions), haematological (thrombocytopenia, agranulocytosis), cardiac (hypotension, tachycardia) and metabolic (hyponatraemia) effects. The re-assessment of tianeptine pharmacovigilance data in 2012 led to several adverse effects being added to the SPC: hyponatraemia, increased liver enzymes, hepatitis, that can, in exceptional cases, be severe, extrapyramidal symptoms and involuntary movements, confusion, hallucinations and exceptional bullous reactions.

Tianeptine is associated with the risk of abuse and drug dependence estimated by the National Narcotics and Psychotropics Committee to be 1 case per 1000 patients treated. According to an analysis of reimbursement data from the EGB 2006-2010, 8% of regular users (patients receiving at least 12 reimbursements for STABLON over a year) received an average estimated dosage of over 50 mg daily and 2.4% received an estimated daily dosage of over 75 mg (the recommended dose is three tablets per day, which is equivalent to 37.5 mg). In 2011, in view of the drug dependence data, the National Narcotics and Psychotropics Committee requested a re-assessment of the benefit/risk balance of tianeptine.
In February 2012, the National Marketing Authorisation Committee concluded that the benefit/risk balance for tianeptine remained positive although it tightened the prescribing and dispensing conditions of STABLON. Since 3 September 2012 STABLON has been subject to part of the narcotics regulations (secure prescription, prescription length restricted to 28 days).
The impact of this measure will be assessed one year after its introduction (September 2013).
The National Marketing Authorisation Committee also asked the company to conduct a clinical study in the elderly.

010 THERAPEUTIC USE

Antidepressants are the reference pharmacological treatment for moderate to severe major depressive episodes. The diagnosis of a major depressive episode should be made following the international classification criteria (DSM-IV, ICD-10). The severity of symptoms is defined on the basis of an evaluation of the number, severity and consequences of the depressive symptoms.

Antidepressants are not recommended in mild typical depressive episodes or for depressive symptoms which do not represent major depressive episodes (isolated or insufficient number of symptoms to meet the DSM criteria or depressive symptoms present for less than 15 days).

According to the ANSM (formerly Afssaps) 2006 recommendations[9], on an ambulatory basis except in specific cases, a selective serotonin reuptake inhibitor (SSRI), a serotonin and noradrenaline reuptake inhibitor (SNRI) or antidepressant belonging to the "other antidepressant" class (the class to which tianeptine belongs) should be prescribed as first-line because of their greater safety. An imipramine derivative or MAOI should be prescribed as second- or third-line therapy.

Antidepressant therapy should not be considered independently of overall management and must be combined with psychotherapy.

Concomitant somatic diseases and their treatments and the risk of therapeutic interactions should be considered, particularly in the elderly.

If tianeptine is prescribed, patients should be monitored particularly for the risk of abuse and dependence. The benefit of prescription must be assessed very carefully in subjects with a past history of drug or alcohol dependence in view of the increased risk of abuse or dependence in these patients.

[9] Bon usage des médicaments antidépresseurs dans le traitement des troubles dépressifs et des troubles anxieux de l'adulte. Afssaps, October 2006.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Re-assessment of actual benefit

A major depressive episode is characterised by a depressive mood or loss of interest or pleasure in almost all activities. The level of functional deterioration associated with the major depressive episode varies although stress and/or a decline in social or occupational life is seen even in mild cases. The most serious consequences of a major depressive episode are attempted suicide and suicide.
Tianeptine is a symptomatic treatment for major depressive episodes.
The efficacy/adverse effect ratio for tianeptine is moderate.
Tianeptine is a first-line medicinal product.
The alternative treatments are other antidepressants indicated for the treatment of major depressive episodes.

> Public health benefit:
> Major depressive episodes are a major public health burden.
> The improvement in their management is a public health need.
> However, in light of available data and given the existing alternative treatments and identified problems of drug dependence, the proprietary medicinal product STABLON does not offer a public health benefit.

Taking account of these points, the Committee considers that the actual benefit of STABLON remains substantial in major depressive episodes (i.e. typical).

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of proprietary products approved for hospital use in the indication "major depressive episodes (i.e. typical)" and at the dosages in the Marketing Authorisation.

◗ Reimbursement rate: 65%

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
The packaging in boxes of 30 tablets is unsuitable for the dispensing conditions of STABLON which must be dispensed as a narcotic and subject to a prescription length not exceeding 28 days.

◗ Other requests
The Transparency Committee wishes to be informed of the results of the clinical study in elderly subjects being carried out at the request of ANSM (clinical report expected in October 2016).

Appendix

References

Alby J.M., Ferreri M., Cabane J., De Bodinat C., Dagens V. Efficacy of Tianeptine (STABLON®) for the treatment of major depression and dysthymia, with somatic complaints. Comparative trial compared with fluoxetine (Prozac®). Ann Psychiatr 1993a; 8 (2): 136-144.

Ansseau M, Bataille M, Briole G. Controlled comparison of tianeptine, alprazolam and mianserin in the treatment of adjustment disorders with anxiety and depression. Human Psychopharmacology 1996; 11: 293-298.

Brion S, Audrain S, De Bodinat C. Major depressive episodes in subjects over 70 years of age. Efficacy and acceptability of tianeptine vs mianserin. Presse Med 1996; 25:461-468.

Cassano GB, Heinze G, Loo H, Mendlewicz J, Paes De Sousa M. A double-blind comparison of tianeptine, imipramine and placebo in the treatment of major depressive episodes. European Psychiatry 1996, 11: 254-259.

Chaby L, Grinsztein A, Weitzman JJ, De Bodinat C, Dagens V. Tianeptine vs maprotiline in menopausal and premenopausal anxiety and depression: a double blind efficacy and acceptability study. Presse Med 1993; 22: 1133-1138.

Chapuy P, Cuny G, Delomier Y, Galley P, Michel JP, et al. 1-year open study of tianeptine in 140 elderly patients with depression. Presse Med 1991, 20 (37): 1844-1852.

Costa E Silva JA, Ruschel SI, Caetano D, Rocha FL, Da Silva Lippi JR. Placebo-controlled study of tianeptine in major depressive episodes. Neuropsychobiology 1997, 35: 24-29.

Dalery J, Dagens Lafont V, De Bodinat C. Therapeutics efficacy of tianeptine vs placebo in the long-term treatment (16.5 months) of unipolar major recurrent depression. L' Encephale 1997; 23: 56-64.

Dalery J, Dagens-Lafont V, de Bodinat C. Efficacy of tianeptine vs placebo in the long-term treatment (16.5 months) of unipolar major recurrent depression. Human Psychopharmacology Clin Exp 2001; 16: S39-S47.

Grivois H. Double-blind controlled trial of the therapeutic value of tianeptine in depression in alcoholics hospitalized for treatment of alcoholic addiction. Biol. Psychiatry 1981, 5: 601-604.

Guelfi JD, Pichot P, Dreyfus JF. Efficacy of tianeptine in anxious-depressed patients: results of a controlled multicenter trial versus amitriptyline. Neuropsychobiology 1989; 22: 41-48.

Invernizzi G, Aguglia E, Bertolino A, Cassacchia M, Ciani N, et al. The efficacy and safety of tianeptine in the treatment of depressive disorder: results of controlled double-blind multicentre study compared with amitriptyline. Neuropsychobiology 1994, 30: 85-93.

Kasper S, Olie JP. A meta-analysis of randomized controlled trials of tianeptine compared with SSRI in the short-term treatment of depression. Eur Psychiatry. 2002; 17 (Suppl 3): 331-40.

Lépine JP, Altamura C, Ansseau M, Ayuso Gutierrez JL, Bitter I, et al. Tianeptine and paroxetine in major depressive disorder, with a special focus on the anxious component in depression: an international, 6-week double-blind study. Human Psychopharmacology, Clinical and Experimental 2001b; 16: 219-227.

Lôo H; Saiz Ruiz J; Costa E Silva JA. Efficacy and safety of tianeptine in the treatment of depressive disorders in comparison with fluoxetine. Human Psychopharmacology 2001; 16:S31-S38.

Lôo H; Saiz Ruiz J; Costa E Silva JA. Efficacy and safety of tianeptine in the treatment of depressive disorders in comparison with fluoxetine. J Affect Disord 1999; 56: 109-118.

Lôo H, Hantzberg P., Defrance R, Kamoun A, Deniker P. Treatment with tianeptine of depressive syndromes in drug addicts after withdrawal: assessment of efficacy and investigation of dependence. L'Encéphale 1987; 13: 295-299.

Lôo H, Malka R, Defrance R, Barrucand D, Bernard JY. Tianeptine and amitriptyline: controlled double-blind trial in depressed alcoholic patients. Neuropsychobiology 1988; 19: 79-85.

Malka R, Loo H, Ganry H, Souche A, Marey C et al. Long-term administration of tianeptine in depressed patients after alcohol withdrawal. Br. J. Psychiatry 1992; 160 (suppl. 15): 66-71.

Nickel T, Sonntag A, Schill J. Clinical and neurobiological effects of tianeptine and paroxetine in major depression. J Clin Psychopharmacol 2003; 23: 155-168.

Novotny V, Faltus F. Tianeptine and fluoxetine in major depression: a 6-week randomised double-blind study. Human Psychopharmacol Clin Exp 2002; 17; 299-303.

Ostaptzeff G. Double-blind controlled trial compared with imipramine of the efficacy of tianeptine in non-psychotic depression. Biol Psychiatry 1981; 597-600.

Saiz-Ruiz J, Montes JM, Alvarez E, Cervera S, Giner J, et al. Tianeptine therapy for depression in the elderly. Prog. Neuropsychopharmacol. Biol. Psychiatry 1998; 22: 319-329.

Szadoczky E, Furedi J. Efficacité et tolérance de la tianeptine et de la sertraline dans le traitement d'attaque de la dépression. L'encéphale 2002; XXVIII: 343-9, cahier 1.

Waintraub L, Septien L, Azoulay P. Efficacité et tolérance de la tianeptine dans les épisodes dépressifs majeurs. Etude contrôlée versus paroxétine sur 3 mois. CNS Drugs 2002; 16 (1): 65-75.

Weiss C, Gorceix A, Kindynis S. Double-blind controlled trial versus nomifensine of the activity and onset of action of a new antidepressant: Tianeptine. Biol Psychiatry 1981; 5: 593-596.