HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

29 November 2006

NEBIDO 1 000 mg/4 ml, injectable solution
B/1 ampoule (CIP: 367 582-7)

Applicant : SCHERING S.A Laboratory

Testosterone undecanoate

List I

Date of the Marketing Authorisation (mutual recognition procedure): 21 January 2005

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

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

testosterone undecanoate

1.2. Indication

Replacement therapy for forms of male hypogonadism where testosterone deficiency has been confirmed clinically and biologically.

1.3. Dosage and method of administration

Via the intramuscular route.

Adults and elderly subjects

Inject one ampoule of NEBIDO (equivalent to 1 000 mg testosterone undecanoate) every 10 - 14 weeks. Injections at these intervals make it possible to maintain adequate testosterone levels and do not result in accumulation.

The injections must be performed very slowly. NEBIDO must be injected deeply into the buttock muscle. The usual precautions for intramuscular administration have to be taken. The utmost care should be taken to avoid intravascular injection. The contents of an ampoule must be injected intramuscularly immediately after opening the ampoule.

Initiation of treatment

Serum testosterone levels must be determined before the start of treatment and during the initiation phase. Depending on serum testosterone levels and clinical symptoms, the interval after the first injection may be reduced to a minimum of 6 weeks instead of the recommended interval of 10 - 14 weeks for maintenance therapy. This loading dose will make it possible to achieve adequate serum testosterone levels more rapidly.

Follow-up and tailoring of the treatment to individual needs

The recommended interval between injections is 10 – 14 weeks. Close monitoring of serum testosterone levels is required during the maintenance therapy. It is advised to regularly measure the serum testosterone level. These determinations must be performed at the end of the interval between two injections and take into account the clinical signs. These serum levels must be in the lower third of normal values.
Where serum levels are below normal, the interval between 2 injections must be shortened. Where levels are high, prolongation of the interval between 2 injections may be considered.

Children and adolescents

NEBIDO is not indicated in children and adolescents and has not been the subject of clinical studies in boys under the age of 18 years.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2006)

G	Genitourinary system and sex hormones
G03	Sex hormones and genital system modulators
G03B	Androgens
G03BA	3-oxoandrosten derivates
G03BA03	testosterone

2.2. Medicines in the same therapeutic category

Testosterone-based medicinal products administered via:

Injectable route: ANDROTARDYL 250 mg (testosterone enanthate),
1 intramuscular injection every 3 weeks

Oral route: PANTESTONE 40 mg (testosterone undecanoate),
2 - 4 tablets every 24 hours

Transdermal route: TESTOPATCH 1.2 mg/24 h, 1.8 mg/24 h and 2.4 mg/24 h. (testosterone)
Two transdermal devices must be applied simultaneously to the skin, arm, lower back or thighs, and renewed every 48 hours.

Reminder: the following medicinal products are not reimbursable:

Cutaneous route: ANDROGEL 25 mg/50 mg (testosterone)
1 - 2 doses every 24 hours
ANDRACTIM (androstanolone)[1]
1 - 2 doses every 24 hours

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The laboratory has filed the findings of 4 studies:

- three pharmacokinetic studies which will not be detailed in the opinion;
- one unpublished phase III randomised, open-label study designed to compare the efficacy and tolerance of NEBIDO (1 injection of 1,000 mg every 6 weeks for the first 3 injections, followed by a final injection 9 weeks later) with the efficacy and tolerance of ANDROTARDYL (1 injection of 250 mg every 3 weeks) in 40 hypogonadic men (20 patients in each treatment group, blood testosterone < 5 nmol/l), aged 18 – 65 years, treated for 30 weeks.

There has been an open 2 years follow-up of the study.

The study primary endpoints were changes in erythropoiesis (changes in haemoglobin and haematocrit levels) and changes in the prehensile force of the hands (measured using a dynamometer) between beginning and end of the treatment in each group.

The secondary assessment endpoints were patient well-being assessed on the basis of a visual scale, sexual activity, bone density, serum levels of testosterone, dihydrotestosterone, oestradiol, LH, FSH, etc.

According to the experts, assessment of clinical symptoms (such as sexual disorders, although all symptoms of hypogonadism are not very specific) or general well-being with a quality-of-life scale would have been more appropriate.

Assessment of changes in serum levels of total testosterone in an equivalence or superiority study versus ANDROTARDYL would have been more relevant.

In patients following a long-term androgenic treatment, the following biological parameters (haemoglobin, haematocrit, hepatic function) must be monitored regularly in addition to

[1] Reimbursable for its indication of gynaecomastia

follow-up of blood testosterone. The choice of these biological parameters as primary efficacy endpoints is not relevant.

Results (in ITT population):

	NEBIDO (n=20)		ANDROTARDYL (n=20)	
	Baseline	At weeks 30	Baseline	At weeks 30
Mean haemoglobin (g/dl)	14.35	15.70	14.73	15.9
Haematocrit (%)	43.4	46.8	44.4	47.8
Mean prehensile force of left hand (Kp)	37.5	41.4	44.6	48.9
Prehensile force of right hand (Kp)	40.1	44.1	47.5	51.2

These is no comparison test for the 2 treatment groups available.

Comments:
No hypothesis (of superiority or equivalence) has been formulated and no determination of sample size has been performed for this study. Furthermore, the number of patients included is small and the length of treatment relatively short for a treatment normally initiated for life.

Analysis of this study has been exploratory and descriptive, and no statistical test performed.

Given the inadequate methodological quality of this study and the endpoints analysed, the Transparency Committee cannot take its results into consideration for the purpose of assessing the level of effect.

The Transparency Committee regrets the absence of relevant comparative data related to efficacy and tolerance versus ANDROTARDYL or another route of administration of testosterone.

3.2. Adverse Effects

During the clinical studies conducted with NEBIDO
The adverse effect most frequently reported was pain at the injection site.

Adverse effects reported during the clinical studies *(frequency [>1/100 ,< 1/10])* and associated with the treatment were as follows: diarrhoea, arthralgia, pain in the legs, dizziness, excessive sweating, headache, respiratory disorders, acnea, breast pain, gynaecomastia, pruritus, skin complaints, testicular pain, prostate disorders, and subcutaneous bruising at the injection site.

Tolerance described in the literature with preparations containing testosterone:
- haematological disorders: rare cases of polycythaemia (erythrocytosis) ;
- metabolic disorders: weight gain, changes in electrolytes (retention of sodium, chlorine, potassium, calcium, inorganic phosphates) and water retention during high-dose and/or prolonged therapy ;
- nervous system disorders: nervousness, aggressiveness, depression ;
- skin and subcutaneous tissue disorders: acne, seborrhoea and alopecia ;
- reproductive system disorders: impairment of libido; increase in the frequency of erections. High doses of testosterone frequently induce a reversible interruption or reduction of spermatogenesis, manifesting itself in a reduction in the size of the testicles. In addition, replacement testosterone therapy for male hypogonadism may,

in rare cases, lead to persistent and painful erections (priapism), prostate anomalies, prostate cancer[2], and urinary obstruction
- - hypersensitivity reactions
- - muscle cramps
- - sleep apnoea
- - very rare cases of icterus and hepatic function test disorders.

3.3. Conclusion

The phase III comparative, randomised, open-label study filed by the company does not make possible the level of NEBIDO's effect assessment compared with that of ANDROTARDYL, given its inadequate methodology (no statistical hypothesis formulated, irrelevant primary endpoints, no statistical testing).

The Transparency Committee regrets the absence of relevant comparative data.

The tolerance profile for NEBIDO is acceptable and identical to that usually found for testosterone-based proprietary pharmaceutical products.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Male hypogonadism (hypo- or hypergonadotrophic) is defined by a testosterone deficiency which may manifest itself in clinical signs (regression of secondary sexual characteristics, change in body composition, asthaenia, loss of libido, erectile dysfunction, mood disorders, osteopaenia which may develop into fracturing osteoporosis, etc.)[3] that reduce quality of life and may cause disability.

NEBIDO is a replacement hormone therapy for symptomatic purposes.
Its efficacy/adverse effects ratio is high.
This proprietary pharmaceutical product is a first-line treatment.
There are drug-based therapeutic alternatives.

Public Health Benefit:
Male hypogonadism suitable for replacement therapy places a limited burden on public health (patients with hypogonadism of genetic origin or acquired by organic damage to the testicles or hypothalamus and pituitary system).

Improvement of the treatment of hypogonadism represents a therapeutic need but is not directly a public health priority.

Considering available data and taking into account existing therapies, no impact in terms of morbidity or quality of life is expected for this proprietary pharmaceutical product.

Furthermore, the expected benefit for the population cannot be reliably predicted for this proprietary pharmaceutical product given, in particular, the unknown factors concerning the impact of this sustained-release form of testosterone on the health of treated patients, risks of misuse which, as with all replacement androgen therapy, cannot be ruled out and the conditions for placement under treatment which are still a

[2] The data relating to the risk of prostate cancer associated with testosterone therapy do not allow conclusions to be drawn about a causality relationship.
[3] EAU (European Association of Urology) Guidelines Investigation, treatment and monitoring of late-onset hypogonadism in males ISA, ISSAM, and EAU Recommendations Nieschlag 2005 ISSAM

matter for discussion (there is no consensus concerning normal values for blood testosterone as a function of age).

As a result, given current knowledge, no public health benefit is expected for the proprietary pharmaceutical product NEBIDO.

The actual benefit is substantial

4.2. Improvement in actual benefit

The study filed has an inadequate methodology and does not make it possible to determine the level of effect of NEBIDO compared with ANDROTARDYL. As a result, NEBIDO does not improve actual benefit (IAB V) compared with ANDROTARDYL but makes an additional therapeutic contribution in replacement therapy for male hypogonadism.

4.3. Therapeutic use

Approach to hypogonadism [4, 5]

The aim of hormone therapy with testosterone (replacement androgen therapy, reference treatment of adult male hypogonadism) is to improve, in particular, sexual disorders, sense of well-being, bone mineral density, etc. by returning serum testosterone levels to values considered as normal. The variability of results between various laboratories, all assays must be performed by the same laboratory for a subject. There is currently no consensus about the normal values for blood testosterone according to age. Nevertheless, it should be kept in mind that physiological blood testosterone values decline with age.

Treatment should be initiated only if hypogonadism has been confirmed clinically and biologically and if potential alternative aetiologies have been ruled out. The testosterone deficiency must be demonstrated by clinical signs (regression of secondary sexual characteristics, change in body composition, asthaenia, loss of libido, erectile dysfunction, etc.) and confirmed by 2 separate determinations of blood testosterone. Treatment should not be initiated where prostate cancer is suspected or confirmed.

Certain clinical signs, suchas irritability, nervousness, weight gain, and prolonged or frequent erections, may indicate excessive androgenisation and require dose adjustment.

Replacement androgen therapy is normally a treatment for life and must lead to at least annual checks on the prostate and breasts by recommended methods (rectal palpation and determination of PSA). In men over the age of 40 and in high-risk patients (clinical or familial factors), these checks should be carried out every 3 months for the first year, then every year.

Late-onset hypogonadism in men (or andropause) is indicated in the Marketing Authorisation. However, unlike in young hypogonadic patients for whom the benefit of androgen therapy is fully recognised, the expected gains are not so clear for elderly males, whose androgenic deficiencies are not so straightforward. No studies are available concerning the long-term complications of replacement androgen therapy in elderly patients presenting an androgenic deficiency.[6]

Furthermore, the SPC mentions that experience of the use of NEBIDO among the over-65s is limited. Thus, the use of NEBIDO does not seem appropriate for treating age-related androgenic deficiency.

[4] Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society Clinical Practice Guideline 2006

[5] Cuzin et al. Diagnostic, traitement et surveillance de l'hypogonadisme de survenue tardive chez l'homme : recommandations officielles de l'International Society for the study of the aging male (ISSAM) et commentaires. Progrès en urologie (2004), 14, 1-14

[6] IBID

Several methods of administering testosterone or its derivatives are available, namely the intramuscular, oral and subcutaneous routes. All preparations cannot claim to reproduce the physiological nyctohemeral cycle for testosterone production. The benefit of reproducing this cycle has not, however, been established. The choice of the method of administration must be a joint decision between the patient and the physician. There are currently no observational data for testosterone, whatever the method of administration.

Place of NEBIDO in therapeutic administration strategy
NEBIDO makes an additional therapeutic contribution to adult male hypogonadism approach by reducing the frequency of injections compared with ANDROTARDYL. The Transparency Committee does not recommend the use of NEBIDO during andropause, but only for clear cases of hypogonadism (primary hypogonadism arising from testicular damage or secondary hypogonadism arising from hypothalamic/pituitary insufficiency).

Risk of non-indicated use and misuse
NEBIDO is not indicated for the treatment of male sterility or impotence.

Testosterone-based proprietary pharmaceutical products risk to be used for aesthetic purposes or for enhancing physical performance outside any medical indication represents misuse.

4.4. Target population

There are no French epidemiological data which make it possible the target population (expert opinion) estimation.

According to a foreign study (Conway 2000), male hypogonadism defined by an androgen deficiency is thought to affect 1 in every 200 men, or, extrapolated to France (men over the age of 18 and below the age of 65), around 90 000 individuals. Nevertheless, this population should be smaller and limited to adult male subjects with clinically and biologically confirmed hypogonadism (blood testosterone below 2 ng/ml – expert opinion). Patients suitable for treatment with NEBIDO would be those with clear hypogonadism (primary hypogonadism arising from testicular damage or secondary hypogonadism arising from hypothalamic/pituitary insufficiency) and not an age-related androgenic deficiency.

4.5. Recommendations of the Transparency Committee

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the Marketing Authorisation.

The Transparency Committee is in favour of a restriction on the conditions concerning initial prescription. The Transparency Committee will give its opinion at the end of the process of redefining conditions for the prescription of androgens which is being undertaken by the French Health Products Safety Agency (AFFSaPS).

The Transparency Committee does not recommend the use of NEBIDO in connection with age-related androgenic deficiency.

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%