HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

Opinion

9 May 2007

**ATARAX 2 mg/ml, syrup**
**Fl/200 ml (CIP: 300 814-3)**

**ATARAX 25 mg, scored tablet**
**B/30 (CIP: 300 813-7)**

**Applicant: UCB PHARMA**

Hydroxyzine
N5BB01
List I
The duration of prescription of this medicinal product should not exceed 12 weeks.

Date of Marketing Authorisation:
Initial MA: 16/08/1988
30 August 2006: extension of indication

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication: "*In children over 3 years, second-line treatment of sleep-onset insomnia caused by a state of hyper-arousal (increased alertness due to anxiety at bedtime), after failure of behavioural measures alone.*"

Health Technology Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

Hydroxyzine

## 1.2. Indications

- Minor manifestations of anxiety;
- Premedication before general anaesthesia;
- Symptomatic treatment of urticaria;
- **In children aged over 3 years (syrup form) and over 6 years (25-mg tablet form) second-line treatment of sleep-onset insomnia caused by a state of hyper-arousal (increased alertness due to anxiety at bedtime) after failure of behavioural measures alone.**

## 1.3. Dosage

The tablet is not an appropriate form for children aged less than 6 years (risk of choking).

In sleep-onset insomnia in children over 3 years, the dosage proposed as an indication is 1 mg/kg/day, and treatment should be short lasting (not more than 2 weeks).

# 2 SIMILAR MEDICINAL PRODUCTS

## 2.1. ATC Classification (2006)

| | |
|---|---|
| N: | Nervous system |
| N05: | Psycholeptics |
| N05B: | Anxiolytics |
| N05BB: | Diphenylmethane derivatives |
| N05BB01: | Hydroxyzine |

## 2.2. Medicines in the same therapeutic category

H1 antihistamines indicated in insomnia in the child are:

- NOPRON, syrup 15 mg/5 ml (niaprazine, phenothiazine derivative): “treatment of occasional insomnia in children aged over 3 years”.
- THERALENE, 5 mg tablet, 5 mg/10 ml syrup and 1 mg/drop oral solution (alimemazine, phenothiazine derivative): “transient and occasional insomnia” in children from 3 years for oral solutions and 6 years for tablets.
- TEYSSEDRE SYROP (alimemazine) (not reimbursable).
- PHENERGAN, tablet 25 mg (promethazine, phenothiazine derivative): This is only indicated in “transient and occasional insomnia ” in its tablet form which is reserved for adults. The syrup form, more suitable for children, does not have the indication.

## 3 ANALYSIS OF AVAILABLE DATA

UCB PHARMA provided no study specifically evaluating hydroxyzine in the indication concerned by this opinion.

The data presented by the company are based on two studies (SIMONS 1984 and SIMONS 1996) and on a collection of pharmacovigilance data.

1/ The two studies provided by the company[1,2] are old. They included a small number of patients (12 and 15 children) and concerned indications which are not sleep onset disorders in children:

- The objective of the SIMONS study 1984[3,] was to evaluate the pharmacokinetics of hydroxyzine in the child and its efficacy in the treatment of allergic skin reactions;
- The objective of the SIMONS study 1996[4] was to evaluate the effects of hydroxyzine and diphenhydramine on the central nervous system in children with allergic rhinitis.

These two studies are not therefore discussed in this opinion.

2/ The company also submitted with the dossier a review of safety data of different H1 antihistamines[5] (review by SIMONS 1994) confirming that the group of first generation H1 antihistamines including hydroxyzine, frequently causes drowsiness and CNS disorders.
Moreover, since it was first marketed in 1955, 212 adverse reactions have been reported internationally in children aged from 30 months to 15 years, including 25 cases in France.
The most often reported reactions were CNS disorders including cases of drowsiness/sedation (11), convulsions (5) and consciousness disorders (4).
The most frequently observed adverse reaction is drowsiness.

A MA was obtained after an application to AFSSAPS and is based on the pharmacological properties of the medicinal product and its expected efficacy because of practitioners' knowledge of the sedative effect of hydroxyzine, and the unanswered therapeutic need.

[1]Simons et al. Pharmacokinetics and antipruritic effects of hydroxyzine in children with atopic dermatitis. The journal of pediatrics. 1984 (vol. 104), n°1: 123-127.
[2]Simons et al. Adverse central nervous system effects of older antihistamines in children. Pediatr Allergy Immunol 1996: 22-27.
[3]Simons et al. Pharmacokinetics and antipruritic effects of hydroxyzine in children with atopic dermatitis. The journal of pediatrics. 1984 (vol. 104), n°1: 123-127.
[4]Simons et al. Adverse central nervous system effects of older antihistamines in children. Pediatr Allergy Immunol 1996: 22-27.
[5]Simons. H1-receptors antagonists, comparative tolerability and safety. Drug Safety 1994. 10 (5): 350-380.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual Benefit

Sleep-onset disorders generally do not cause any serious complication or disability, but if they persist they may result in a marked deterioration in quality of life.

These proprietary products are intended for symptomatic treatment.
The efficacy/safety ratio of these proprietary products is moderate.

These proprietary products are second-line medicinal products to be used after failure of behavioural measures alone.
There are alternative pharmacological and non-pharmacological therapies to these proprietary products.

In terms of public health, (despite the high incidence of these disorders), the burden represented by sleep-onset insomnia of the child is small taking into account its generally benign nature.
Although, in the case of failure of behavioural therapy, there is a therapeutic need in children with sleep-onset insomnia (in particular a need for medicinal products with no side effects (neuropsychocognitive effects)), the improved management of these disorders is not a public health need.
A review of the available data shows that the expected impact of this proprietary medicine in terms of morbidity and quality of life (due to its probable improved safety with respect to existing medicines) cannot be quantified.

Consequently, ATARAX is not expected to benefit public health in this indication.

The actual benefit of ATARAX is low in this indication.

### 4.2. Improvement in actual benefit

ATARAX does not improve actual benefit (IAB V) in the usual management of children aged over 3 years, for second-line treatment of sleep-onset insomnia caused by a state of hyper-arousal (increased alertness due to anxiety at bedtime), after failure of behavioural measures alone.

### 4.3. Therapeutic use[6,7]

Sleep disorders in children are rarely considered to be a specific pathological entity.

The main problem is to distinguish between “normal” and “pathological” sleep onset disorders in children. This distinction is very subjective and mainly depends on parents’ awareness of this problem, their expectations and interpretation of sleep behaviour though cultural and familial backgrounds also play a considerable role.

The aetiologies of sleep onset disorders in children are mainly behavioural (75% of cases). In many cases in young children, they are in caused by negative conditioning towards sleep onset. The initial therapeutic strategy must therefore involve behavioural and educational measures.

These behavioural measures primarily consist of imposing a good sleep hygiene: favourable surroundings, appropriate bed and rising times, avoidance of stimulating activities before bedtime. The cognitive and behavioural approach is particularly useful when a change in parents’ behaviour is expected.

According to the experts, sleep disorders represent the first reason for prescribing psychotropic drugs in children aged under 3 years in France, and early exposure to psychotropics may be a risk factor leading to an excessive consumption of hypnotics at adult age. Medication with hydroxyzine should therefore only be used for children in exceptional cases, with the shortest possible duration (not more than 2 weeks), and must only be attempted after a long discussion with the parents. It should be instituted for second line therapy, in certain forms of sleep-onset insomnia caused by a state of hyper-arousal, in the case of failure of behavioural treatment only. In this case, there are few alternative therapies which are not without risk: risks of extrapyramidal and psychocognitive neurological effects with phenothiazines.

Hydroxyzine is not a suitable treatment either for insomnia of neurological origin, or for certain forms of insomnia with an organic cause, or for insomnia with a psychiatric origin.
The Transparency Committee has no data about the possible impact of hydroxyzine on the pattern of the sleep cycle in children.

### 4.4. Target population

The prevalence of sleep disorders in children is approximately 25% for all ages together: 25 to 50% in preschool children and, 15% to 37% in children of school age.

According to the experts, the target population concerned by the use of hydroxyzine after failure of behavioural measures alone is approximately 10% of children with a sleep disorder.
After reviewing current data, the French Transparency Committee is not able to precisely determine this population.

[6] Report on the topic of sleep. Minister of Health and Solidarity. December 2006
[7] Owens J *Centre d’Excellence pour le développement des jeunes enfants*. Services et programmes efficaces pour gérer les troubles du sommeil des enfants et des nourrissons ainsi que leurs impacts sur le développement social et émotif des jeunes enfants (0 – 5 ans). Encyclopédie sur le développement des jeunes enfants. (27 April 2004).

## 4.5. Transparency Committee Recommendations

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 new indication pending the reassessment of other proprietary medicines indicated in sleep disorders of children.

4.5.1. Packaging:

The treatment of sleep onset disorders should not exceed 2 weeks. The Transparency Committee therefore asks for more appropriate packaging of the proprietary products ATARAX 2 mg/ml (200 ml bottle) and ATARAX 25 mg scored tablets (pack of 30 tablets) to be available in to facilitate good medication use.

4.5.2. Reimbursement rate: 35%