



HAUTE AUTORITÉ DE SANTÉ

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

**TRANSPARENCY COMMITTEE**

OPINION

27 April 2011

Review of the dossier for a proprietary medicinal product listed for a limited duration in accordance with the Decree of 27 October 1999 (Official Journal dated 30 October 1999) and the Order of 8 December 2005 (Official Journal dated 29 December 2005)

**MEPRONIZINE 400 mg/10 mg, scored coated tablets  
B/30 (CIP code: 306 585-6)**

**MEPRONIZINE 400 mg/10 mg, scored coated tablets  
B/50 (CIP code: 559 005-8)**

**Applicant: SANOFI-AVENTIS FRANCE**

Meprobamate, aceprometazine

ATC code: N05CX01 (hypnotics and sedatives in combination, excluding barbiturates)

List I

Date of Marketing Authorisation (national procedure): 23 July 1963 (licence), 16 September 1986 (Marketing Authorisation confirmed)

Amendments:

- 14 November 2005 – Changes to 4.4, Precautions for use: pregnancy and lactation
- 11 March 2008 – Changes to 4.9, Overdose
- 15 March 2010 – Marketing Authorisation for pack B/5
- 20 May 2010 – Changes to the SPC: Restriction of indication, limitation of dosage and treatment duration, revision of the SPC for H1-receptor antagonists
- 23 September 2010 – Addition to 4.4, Warnings (not recommended in elderly patients, particularly patients aged over 75 years) and to 4.8, Undesirable effects (confusion and/or agitation in elderly patients, rare cases of convulsions).

Reasons for the request:

- Change of listing conditions (B/30 and B/50)
- Renewal of listing for reimbursement by National Health Insurance (B/30)

Medical, Economic and Public Health Assessment Division

## 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Meprobamate, aceprometazine

### 1.2. Indication

"Occasional insomnia in adults when the benefit/risk ratio for benzodiazepines appears to be unfavourable."

### 1.3. Dosage

1 tablet daily.

The dosage should be reduced in elderly subjects and patients with impaired renal or hepatic function.

#### Method of administration

A single daily dose taken in the evening, 15–30 minutes before going to bed.

#### Treatment duration

Treatment duration is 2–5 days.

If the insomnia persists for more than 5 days, treatment should be reassessed.

### 1.4. Special warnings and precautions for use

#### **Special warnings**

##### Related to the diagnosis

Insomnia may have a number of causes which do not necessarily require the use of medicines. If possible, the cause of the insomnia should be identified and any underlying factors treated.

Persistence of insomnia after five days of this treatment may indicate an underlying pathology, and treatment should be reassessed.

##### Sleep apnoea

Like any sedative, meprobamate and aceprometazine are likely to aggravate existing sleep apnoea (increase in number and duration of apnoeas).

##### Risk of accumulation

Like any medicines, meprobamate and aceprometazine remain in the body for a period of about 5 half-lives. In elderly patients or those with impaired renal or liver function, the half-life may be considerably extended. After repeated doses, the medicinal product or its metabolites reach steady-state much later and at a much higher level. The efficacy and safety of the medicinal product can only be assessed after steady-state has been reached. The dosage may need to be adjusted.

##### Related to meprobamate

Withdrawal syndrome may occur after sudden discontinuation of prolonged treatment, particularly at high doses. The dose should therefore be reduced gradually, or if treatment is discontinued suddenly, the patient should be monitored carefully.

##### Related to aceprometazine

In the event of hyperthermia, treatment must be suspended; hyperthermia may be one of the signs of neuroleptic malignant syndrome (pallor, hyperthermia, autonomic nervous system disorders).

### Elderly patients

This medicinal product is not recommended in elderly patients, particularly in patients aged over 75 years, because of the risk of sedation and/or dizziness which may encourage falls (e.g. when getting up during the night), with consequences that are often serious in this population.

### **Precautions for use**

Common to both ingredients of the combination

The sedative action may be potentiated by administration of any other central nervous system depressants (particularly alcohol, hypnotics or opioids).

Elderly patients, patients with renal or hepatic impairment: plasma concentrations are increased and plasma clearance reduced. The dosage should be reduced (increased risk of sedation and hypotension).

The medicinal product should also be used with caution in patients with chronic constipation (risk of paralytic ileus).

It is strongly recommended that alcohol is avoided during treatment with this medicinal product.

### **Other precautions for use:**

#### Related to meprobamate

Myasthenia: increased monitoring is required.

Avoid in patients with acute intermittent porphyria.

#### Related to aceprometazine

Use with caution:

- In patients with Parkinson's disease
- In patients with impaired liver function
- Aceprometazine should be used with caution in patients with certain cardiovascular disorders, because of the quinidine-related, tachycardia-inducing and hypotensive effects of phenothiazines.
- Monitoring (clinical and if necessary electrical) should be increased in epileptics because of the possibility of reduction in the epileptogenic threshold by phenothiazines.

### **1.5. Overdose**

Clinical signs begin 1–3 hours after ingestion in the form of inebriation, drowsiness, coma (calm, hypotonic), respiratory depression and hypothermia. The severity of poisoning depends on the ingested dose and is related to the onset of cardiac circulatory failure, either predominantly vasoplegic or predominantly cardiogenic.

Treatment is symptomatic, in a specialist unit. There is no antidote. [...]

### **1.6. Pharmacodynamic properties**

Meprobamate has anxiolytic, sedative and muscle relaxant properties.

Aceprometazine is a phenothiazine with H1-antihistamine properties responsible for a sedative action, adrenolytic, anticholinergic and antidopaminergic properties.

<b>2. REMINDER OF THE COMMITTEE'S OPINION AND CONDITIONS OF INCLUSION</b>
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Opinion of 19 November 1999

Level of actual benefit: low

### 3. SIMILAR MEDICINAL PRODUCTS

#### 3.1. ATC Classification

N	Nervous system
N05	Psycholeptics
N05C	Hypnotics and sedatives
N05CX	Hypnotics and sedatives in combination, excluding barbiturates
N05CX01	Meprobamate, combinations

#### 3.2. Medicines in the same therapeutic category

There are no other medicinal products which are a combination of an H1-antihistamine (phenothiazine) and a carbamate.

##### Combinations of H1-antihistamine (phenothiazine) + benzodiazepine

- Acepromazine+aceprometazine+clorazepate: NOCTRAN Tablets (15%) – On 3 March 2011 the Marketing Authorisation Committee voted against the continued marketing of this medicinal product.

##### H1-antihistamines

- Alimetazine (phenothiazine): THERALENE tablets, oral solution (15%)
- Promethazine (phenothiazine): PHENERGAN tablets (15%)
- Doxylamine: DONORMYL, LIDENE and NOCTYL tablets (not refundable)

### 4. UPDATING OF DATA MADE AVAILABLE SINCE THE PREVIOUS OPINION

The dossier submitted does not contain any new efficacy data.

#### 4.1. Reassessment by the AFSSAPS of the benefit/risk ratio

In May 2006, the French Healthcare Products Safety Agency (AFSSAPS) asked for a reassessment of the benefit/risk ratio for MEPRONIZINE proprietary medicinal products in the context of review of information for H1-antihistamines indicated in sleep disorders.

The data submitted by the company in November 2006 did not include any efficacy data, in particular concerning any benefit of the combination of the two active ingredients of the medicinal product in the indication. The tolerance data confirmed acute overdoses of meprobamate, which were some of the principal cases of serious overdoses and causes of death by psychotropics, a problem which was referred to the French poison control centres in 2004; 100 of the 308 cases reported by the company since the product was placed on the market concerned overdose (at least 86 intentional cases and 77 cases of coma).

A particular risk had been identified in the age range of patients over 65 years, accounting for 27% of all notifications and 45% of all adverse effects. The most commonly reported adverse effects in this age range were orthostatic hypotension, falls, confusion, reduced vigilance, drowsiness and vasovagal disorders. As these effects are anticipated disorders they are generally under-notified; it is often difficult to determine a causal relationship in elderly patients with multiple disorders who are taking a number of medicines. At that time, sleep disorders were the main indication for prescription in 38.6% of cases; the product was

prescribed concomitantly with other psychotropics in almost all cases (tranquillisers 72%, antidepressants 55% and antipsychotics 23%).

In April 2007, the Marketing Authorisation Committee approved the withdrawal of the marketing authorisation for MEPRONIZINE, but the withdrawal of marketing authorisation was considered to be legally inapplicable.

In July 2009, the severity of voluntary overdose with the combination meprobamate+aceprometazine and the neurological adverse effects of the product observed more particularly in the elderly population led the AFSSAPS to approve the following measures:

- Measures required by the Committee in June 2007 for proprietary medicinal products containing meprobamate:
  - . Restriction of indication to patients with a poor benefit/risk ratio for benzodiazepines
  - . Limitation of pack size to reduce the risk of acute toxicity in the event of overdose
- Limitation of dosage to one tablet a day
- Limitation of treatment duration to five days
- Use of this combination in elderly subjects (particularly the very elderly >75 years) not recommended
- Addition of a warning about the risk of falls in elderly subjects because of greater sensitivity to orthostatic hypotension, sedation and extrapyramidal effects
- Addition of the texts produced after the review of H1-antihistamines indicated in insomnia.

These measures were to be accompanied by the introduction of monitoring of MEPRONIZINE at national level by the CRPV (French Regional Pharmacovigilance Centres) and Lille Poison Control Centre, in line with the monitoring applicable to meprobamate concerning tolerance in use and the impact of the reduced pack size.

#### **4.2. Tolerance data**

The pharmacovigilance data were obtained from:

- the most recent periodic safety update report (PSUR) submitted to the AFSSAPS by the company in November 2010 (covering the period 01 October 2005 to 30 September 2010) as part of the five-yearly renewal process for proprietary medicinal products.
- cases notified to the AFSSAPS for the period 01 October 2005 to 27 March 2011.

According to the sales figures, the estimated exposure to MEPRONIZINE was 262,133,656 treatment-days during the period October 2005 to September 2010: 241,394,386 for boxes of 30 tablets and 20,739,270 for boxes of 50 tablets.

The data analysis carried out by Lille CRPV for the period October 2005 to March 2011 found 365 medically confirmed spontaneous notifications for which a relationship with MEPRONIZINE could reasonably be suggested. 76% of these notifications were serious, representing 894 adverse effects; non-serious cases accounted for 153 adverse effects.

In 78% of cases, the period of treatment, which was given for 25% of cases, was not the period recommended by the Marketing Authorisation; in 21% of cases it was more than a year.

Apart from cases of overdose, the daily dosage (specified for 46% of cases) corresponded to the recommended dosage (one tablet a day) in 67% of cases.

The most frequently identified adverse effects were accidental or unspecified voluntary overdose (34%) and coma (20%). The other serious adverse effects included falls (8%), hypotension (7%) and confusion or disorientation (5%). Disorders of consciousness (drowsiness, impaired consciousness, loss of consciousness) were reported in 10% of cases. In particular, there were 13 cases of inhalation pneumonia and 13 cases of drug dependence/withdrawal. Thirty cases of extrapyramidal disorders were reported, including 25

serious cases. The most commonly reported non-serious adverse effects were falls (9 cases) and overdose (11 cases).

Overdose (134 cases) was the most commonly reported adverse effect over the period (37% of adverse effects recorded). Median patient age was 44 years. Voluntary overdose was identified in 73% of cases. Concomitant use of other psychotropics (neuroleptics, benzodiazepines and/or antidepressants) was associated with most of these overdoses. 53% of the overdoses were associated with coma and 15% were fatal.

The risk of drug dependence appeared to be low (17 cases identified) but was probably underestimated in view of the prescription data.

Patients aged over 65 years accounted for 22% of patients. 85% experienced a serious adverse effect. A majority of these patients were concerned by adverse effects such as falls (64%), confusion and disorientation (60%).

In almost all cases patients were taking multiple medications, particularly psychotropics (benzodiazepines, neuroleptics and/or antidepressants in particular), the effects of which may have been partly responsible for the neurological and psychiatric disorders observed.

#### **4.3. Conclusion**

There is still a risk of overdose or serious adverse effects with the fixed-combination medicinal product MEPRONIZINE, particularly in elderly subjects. Overdose accounts for a third of notifications, half involving coma and 15% being fatal. There are no new efficacy data to support any benefit of MEPRONIZINE in the management of occasional insomnia. Alternative therapies exist with a more favourable benefit/risk ratio in the management of these patients.

### **5. DATA ON THE USE OF THE MEDICINAL PRODUCT**

According to the GERS data supplied by the company, nearly 2 million boxes of 30 tablets were sold in 2010. An estimated 80,000 boxes were sold in hospitals.

According to DOREMA data (IMS-EPPM, moving annual total, November 2010), MEPRONIZINE was the subject of 719,000 non-hospital prescriptions (B/30):

- sleep disorders (40%),
- episodes of depression (20%),
- other anxiety disorders (11%).

The mean dosage was 1.3 tablets a day. Mean duration of treatment was 36 days.

## 6. TRANSPARENCY COMMITTEE CONCLUSIONS

### 6.1. Reassessment of actual benefit

The diagnostic factors that are common to all types of insomnia include complaints such as difficulty falling asleep and/or staying asleep, waking too early, feeling unrefreshed by sleep or poor quality sleep occurring despite good sleeping conditions. These complaints have repercussions during the day related to disturbed sleep at night (e.g. fatigue, social dysfunction, irritability, drowsiness, etc.). These night-time and daytime symptoms must have been present for at least a month.

Sleep disturbance and the associated daytime repercussions may have harmful effects on everyday function and on the onset or worsening of physical or psychological conditions.

MEPRONIZINE is intended as a symptomatic treatment for occasional insomnia.

The efficacy/adverse events ratio for these medicinal products is worse than that of alternative therapies.

Various categories of insomnia have been identified and classified according to the timing or presumed aetiology of the sleep disorders (DSM-IV, ICSD-2<sup>1</sup>). In all cases of insomnia, it is important to ensure that the insomniac patient has properly understood and is observing the basic rules of sleep hygiene in terms of times for going to bed and getting up, environmental factors (noise, light, temperature), time spent in bed, physical activity, and taking stimulants at the wrong time.

If hypnotics are prescribed, this must be part of a short-term strategy. A strategy for stopping these medicines should be established from the outset with the patient.

Therapies with benzodiazepines or related substances, which are indicated in severe sleep disorders in the context of occasional insomnia or transient insomnia, are widely prescribed in chronic insomnia, usually for prolonged periods. These treatments may have residual effects, i.e. memory disorders and impaired cognitive function. The benefit/risk ratio in elderly patients has been discussed<sup>2</sup>, particularly in terms of prolonged treatment (off-label) which is made more likely by substance dependence. Antihistamine sedatives are not recommended for elderly patients. The indication for Circadin is limited to primary insomnia in patients aged over 55 years. Herbal remedies may be used for minor sleep disorders.

Non-drug techniques are little used in France and are therefore relatively inaccessible. They are particularly indicated for chronic insomnia (primary or secondary) but may be offered in cases of occasional and transient acute adjustment insomnia (linked to a stressful event or a new situation that is equivalent to a stressor), to prevent the problem becoming chronic. These methods include relaxation, biorhythms, and stimulus and sleep restriction.

Cognitive and behavioural therapies combining these approaches are widely recommended by experts in the management of chronic insomnia, particularly primary insomnia.

Some circadian rhythm disorders in elderly patients may improve with light therapy.

Referral to a specialist is required in some specific cases:

- insomnia that is not responding to properly conducted treatment,
- suspected physical cause requiring sleep study (restless legs syndrome, periodic limb movement disorder, respiratory disorders or arrhythmias during sleep),
- chronic unexplained insomnia, which is atypical or particularly complex, with significant daytime repercussions.

<sup>1</sup> The international classification of sleep disorders: Diagnostic & Coding Manual, ICSD-2. 2nd ed. Westchester, Ill: American Academy of Sleep Medicine; 2005.

<sup>2</sup> Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005; 331: 1169-76.

MEPRONIZINE has no place in the treatment strategy for occasional insomnia.

The public health burden of occasional insomnia in adults is small. Improvement in its management is not a public health need.

The actual benefit of this proprietary medicinal product cannot be evaluated as no efficacy data have been submitted on the use of MEPRONIZINE in a real-life setting. In addition, the known misuse of MEPRONIZINE and tolerance data demonstrating a high frequency of serious adverse events, particularly related to overdose, raise the issue of a harmful impact at population level. Overall, the public health benefit contributed by MEPRONIZINE is non-existent or even negative.

The actual benefit contributed by these proprietary medicinal products is insufficient.

## **6.2. Therapeutic use<sup>3,4</sup>**

Not applicable

## **6.3. Target population**

Not applicable

## **6.4. Transparency Committee recommendations**

The Transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance (B/30).

The Transparency Committee does not recommend continued inclusion on the list of medicines approved for hospital use and various public services (B/50).

### **6.4.1 Packaging**

The packs are not suitable for the dosage and treatment duration recommended in the Marketing Authorisation.

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3 Clinical Practice Guidelines. Management of adult patients complaining of insomnia in general practice. HAS clinical practice guidelines, December 2006 [in French]

4 Report on sleep. Ministry of Health and Solidarity. December 2006