



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

**TRANSPARENCY COMMITTEE**

OPINION

17 November 2010

**HELICIDINE 10 PER CENT, syrup**

**125 ml vial (CIP code: 304 765-7)**

**250 ml vial (CIP code: 340 316-4)**

**Applicant: THERABEL LUCIEN PHARMA**

helicideine  
ATC code: R05DB

Date of Marketing Authorisation:  
HELICIDINE, 125 ml: 22 February 1957  
HELICIDINE, 250 ml: 17 February 1992

Reason for request: Review of actual benefit in accordance with article R. 163-12 of the Social Security Code.

## 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Helicidine

### 1.2. Indication

“Symptomatic treatment of non-productive annoying cough.”

### 1.3. Dosage

“Symptomatic treatment must be given for a short period (a few days) only when the cough occurs.

Adults: 2 soup spoons three times a day.

Children: 2 ml/kg/day split into three doses, i.e.

- children weighing 25 to 50 kg (around 8 to 15 years); 3 to 5 soup spoons a day.

- children weighing 15 to 25 kg (around 4 to 8 years); 1 soup spoon three times a day.

- children weighing 12 to 15 kg (around 30 months to 4 years); 2 teaspoons three times a day.”

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1 . ATC Classification

R : Respiratory system

R05 : Cough and cold preparations

R05D : Cough suppressants, excl. combinations with expectorants

R05DB : Other cough suppressants

### 2.2 . Medicines in the same therapeutic category

#### 2.2.1 Comparator medicines

Cough suppressants not containing or combined with an opiate, indicated in the treatment of annoying non-productive coughs in children (aged over 1 year) and adults, formulated as a syrup:

oxeladine: PAXELADINE, syrup, 125 ml (minor ACB)

oxomemazine: TOPLEXIL 0.33 mg/ml, syrup, 150 ml (minor ACB)

SUGAR-FREE TOPLEXIL 0.33 mg/ml, sweetened oral solution containing potassium acesulfame (minor ACB)

### 2.3. Medicines with a similar therapeutic aim

Other cough suppressants indicated for annoying non-productive coughs, including opiate-based substances such as dextrometorphan, pholcodine and codeine (moderate AB).

## 3 ANALYSIS OF NEW AVAILABLE DATA

### 3.1. Efficacy

#### Non-inferiority study comparing helcidine with dextrometorphan:

This is a randomised, single-blind study conducted to demonstrate the non-inferiority of helcidine compared to dextrometorphan syrup in terms of improvement in quality of life assessed after five days of treatment by the CQLQ score<sup>1</sup>.

The patients taking part were aged from 18 to 65. They had to have seen their generalist physician for a persistent dry cough within the past six weeks, but their temperature could not exceed 38.5°C.

Patients with the following characteristics could not take part:

- those taking cough suppressants or painkillers within the 15 days prior to the study
- taking antidepressant treatment in the form of a monoamine oxidase inhibitor (MAOI)
- on antibiotics
- suffering from respiratory failure
- chesty cough
- asthma
- allergy to the components of the two syrups being compared
- smoking more than 10 cigarettes a day
- pregnant women

The patients were randomised to receive either HELICIDINE syrup or a syrup containing 0.3% dextrometorphan (DEXTROCIDINE).

The study was conducted as a single-blind trial because of the different dosages of the two syrups, which the doctor was able to know if the patient mentioned it when attending an appointment:

- helcidine syrup: two soup spoons taken orally three times a day for five days (i.e. two 250-ml vials)
- dextrometorphan syrup: one 5-ml spoonful taken three times a day for five days (i.e. one 150-ml vial)

The primary endpoint was the CQLQ quality-of-life score assessed by the patient after five days of treatment. Helcidine was to be regarded as not inferior to dextrometorphan if the upper limit of the 95% confidence interval of the difference between treatments was below the predetermined non-inferiority threshold (+ 5 points). The analysis was conducted on the per-protocol population (patients having had assessments at D0 and D5 with no major deviation).

#### Results:

A total of 247 patients were included in the study. One patient who did not take his treatment was excluded. Of the other patients, 124 were given helcidine syrup and 132 were given dextrometorphan syrup. Nine patients withdrew from the study prematurely (contact was lost

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<sup>1</sup> "Cough-specific Quality-of-Life Questionnaire": a quality-of-life score validated specifically for cough, comprising 28 statements to which the patient can respond as follows: 1 = strongly disagree, 2 = disagree, 3 = agree and 4 = strongly agree. The maximum overall score is 112, and a difference of at least 10 is regarded as clinically significant. The questions are divided into six groups, assessing physical symptoms, psychosocial consequences, functional capacities, emotional well-being, extreme physical symptoms and fears regarding personal tolerance. The higher the score, the greater the impact of the cough on quality of life.

with two, and seven stopped taking the treatment before the end of the study). Two patients in each group stopped treatment because of an adverse effect.

Thirty-five patients were not included in the per-protocol population, because of a major deviation (12 patients), cessation of treatment (six patients) or because the data was unusable (17 patients). Consequently, the per-protocol population was made up of 221 patients, 109 in the helcidine group and 112 in the dextrometorphan group (the protocol stated that the minimum number of patients required per group was 98 for an alpha risk of 5% and a power of 85%).

➤ Characteristics of patients included

Table 1 describes the characteristics of patients' coughs. The patients seeing their doctor had had a persistent cough for about five days, affecting them both during the day and at night in about 77% of cases. Severe nocturnal and diurnal coughing fits affected approximately 30 and 38% of patients respectively.

**Table 1:** characteristics of patients' coughs on inclusion (ITT population)

		<b>Helicidine</b> (N=124)	<b>Dextrometorphan</b> (N=132)	<b>Total</b> (N=256)
Duration of symptoms (days)	Mean (standard deviation)	4.5 (4.0)	5.1 (4.8)	4.8 (4.4)
When coughing fits occur				
Day	n (%)	19 (15.3)	28 (21.2)	47 (18.4)
Night	n (%)	8 (6.5)	5 (3.8)	12 (5.1)
Day and night	n (%)	97 (78.2)	99 (75.0)	196 (76.6)
Severe daytime coughing fits	n (%)	37 (31.9)	34 (26.8)	71 (29.2)
Severe night-time coughing fits	n (%)	36 (34.3%)	43 (41.3%)	79 (37.8%)

The impact of the cough on patients' activities was measured on inclusion (assessed on a scale of 0 to 10): the median figure for impact on family life, work and social life was 2 to 3 and the impact on sleep was 5.

➤ Results for the primary endpoint (per protocol population)

The CQLQ score fell by  $11.5 \pm 12.6$  points in the helcidine group and  $10.2 \pm 10.2$  points in the dextrometorphan group after five days of treatment.

As the upper limit of the 95% confidence interval of the difference between treatments was below the non-inferiority level of +5, it can be concluded that helcidine is not inferior to dextrometorphan in terms of impact on quality of life assessed by the CQLQ score (see table 2).

**Table 2:** variation in the CQLQ score (PP population)

CQLQ score (0 to 112 points)		Helicidine (N=109)	Dextrometorphan (N=112)
Patients with scores available on D0 and D5 (n)		108	112
D0	Mean (standard deviation)	55.1 (13.4)	53.4 (13.3)
D5	Mean (standard deviation)	43.6 (13.3)	43.2 (13.9)
<b>Difference between helicidine and dextrometorphan on D5</b>		<b>0.4 [-3.2 ; 4.0]</b>	
Change from D0 to D5	Mean (standard deviation)	-11.5 (12.6)	-10.2 (10.2)

The significance of these results is limited since:

- this was a single-blind study;
- this non-inferiority study did not include a placebo arm to demonstrate the internal validity of the study. This is important in the case of cough suppressants as the placebo effect is significant;
- the protocol did not allow for an increase in the dextrometorphan dosage up to the maximum dose indicated in the SPC (six 5-ml doses a day);
- the choice of the CQLQ score as the primary efficacy endpoint is questionable, as:
  1. in the study carried out to validate this score, only 30 out of 184 patients had an acute cough<sup>2</sup>,
  2. no studies have been conducted to investigate the efficacy of dextrometorphan on this score;
- the average variations of the CQLQ score reached the clinical significance threshold of 10 points. However, the standard deviations of these variations are of the same order of magnitude as the variation itself, pointing to a significant inter-patient disparity in the observed effect. This may be related to variations in the severity of symptoms among the patients taking part;
- it would have been useful to consider the change in the primary efficacy endpoint over time in order to show whether one treatment acted faster than the other.

### 3.2. Adverse effects

The treatments were well tolerated in the study described above, which was conducted on adult patients. The only adverse event to occur at a frequency level of over 1% was somnolence in two patients in the dextrometorphan group (n = 132).

The SPC has recently been amended to state that the proprietary drug HELICIDINE is contraindicated in children under two years of age. This change was made in the light of a pharmacovigilance investigation which revealed a risk of pleural effusion and worsening of bronchiolitis in this age group following treatment with mucolytics or helicidine.

Cases of sudden infant death have also been observed in infants being treated with mucolytics or helicidine. Although no causal link has been demonstrated, since there is no detailed context and no associated risk factors are known, the possibility of these drugs being responsible cannot be ruled out.

It should be remembered that all proprietary cough suppressants (oxememazine, chlorphenamine maleate, promethazine hydrochloride, alimemazine, pimethixene, fenspiride)

<sup>2</sup> French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a cough-specific quality-of-life questionnaire Chest. 2002 Apr;121(4):1123-31.

will also be contraindicated for use in children under two years as from 15 March 2011<sup>3</sup>. Centrally-acting cough suppressants (codeine, dextrometorphan, pholcodine, noscapine) are also contraindicated for use in this age group.

A reference to the risk of bronchial effusion in patients unable to expectorate has also been added to the "Adverse effects" section.

HELICIDINE cannot be regarded as the only cough suppressant which is not contraindicated for pregnant women:

The SPC for HELICIDINE does not actually have a section dealing specifically with pregnancy. The situation regarding the use of other cough suppressants by pregnant women is not entirely clear:

- PAXELADINE (oxeladine): the SPC states that no relevant teratogenesis studies have been carried out on animals and that in clinical use no malformation or foetotoxicity has been observed to date. However, the monitoring of pregnancies exposed to oxeladine citrate is insufficient to rule out any risk. Consequently, as a precaution, it is preferable that pregnant women do not take this medicinal product.
- TOPLEXIL 0.33 mg/ml (oxomemazine): the SPC states that this medicinal product is not recommended in the first trimester of pregnancy. No reliable teratogenicity data is available in animals, and no sufficiently relevant data is available to allow any malformation or foetotoxicity effect to be assessed.
- Opiate-based cough suppressants containing codeine or dextrometorphan are not formally contraindicated during pregnancy. The SPCs for these products point out that there is a risk of teratogenicity in animals, which has not been observed in pregnant women. High dosages taken at the end of pregnancy, even for a short time, can lead to respiratory depression in the neonate. Chronic consumption of dextrometorphan by a woman in the last trimester of pregnancy, at any dose, can lead to a withdrawal syndrome in the neonate. It is therefore recommended that these products be used only when essential and for a short period.

The French Centre for Information on Teratogenic Agents, CRAT recommends that, if a woman needs to take a cough suppressant throughout pregnancy, preference should be given to dextrometorphan or codeine, the effects of which on pregnant women are better understood, rather than helcidine.

### 3.3. Conclusion

A randomised, single-blind study conducted on 247 adult patients found helcidine syrup to be not inferior to 0.3% dextrometorphan syrup in terms of improvement in the CQLQ score after five days of treatment. However, the relevance of these findings is limited due to methodological shortcomings (in particular, the lack of a placebo group, the single-blind design, the choice of the primary efficacy endpoint which has been validated on a very small number of patients and for which the impact of dextrometorphan is not known) and the average variations in the CQLQ score between D0 and D5 in both groups, which are of borderline clinical relevance and have significant standard deviations.

Both syrups were well tolerated in this study, carried out on adults.

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<sup>3</sup> AntiH1 proprietary cough suppressants (oxomemazine, chlorphenamine maleate, promethazine hydrochloride, alimemazine, pimethixene, fenspiride) to be contraindicated for children aged under two years as from 15 March 2011. List of medicinal products withdrawn from the market and of medicinal products contraindicated for children aged under two years. Afssaps, November 2010. [http://www.afssaps.fr/Infos-de-securite/Points-d-information/Nouvelle-modalites-de-prise-en-charge-de-la-toux-chez-le-nourrisson-enfant-de-moins-de-2-ans-Point-d-information/\(language\)/fre-FR](http://www.afssaps.fr/Infos-de-securite/Points-d-information/Nouvelle-modalites-de-prise-en-charge-de-la-toux-chez-le-nourrisson-enfant-de-moins-de-2-ans-Point-d-information/(language)/fre-FR)

The findings of a pharmacovigilance investigation, which concluded that there was an increase in the risk of bronchial effusion and worsening of bronchiolitis in very young children (from birth to two years of age) have led Afssaps to contraindicate the use of HELICIDINE in children aged under two.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### **4.1. Re-evaluation of actual benefit**

Annoying non-productive cough is not a serious condition.  
This proprietary drug is part of treatment addressing the symptoms.  
The efficacy/adverse effects ratio of helcidine is low.  
This proprietary drug is a second-line treatment.  
There are treatment alternatives.

The actual benefit of HELICIDINE syrup is low.

### **4.2. Therapeutic use**

Coughs have a varied aetiology. Practitioners should seek and treat the cause where possible before prescribing a cough suppressant.

Only coughs which are annoying can justify cough suppressant treatment targeted solely at the symptoms.

The treatment must be given for a short period (a few days) only when the cough occurs.

If the cough persists despite cough suppressant treatment given at the normal dosage, the practitioner must review the clinical situation rather than increasing the dose.

Fixed combinations of cough suppressants are not recommended as it is difficult to adjust the dosage and multiple adverse effects may occur.

Opiate-based cough suppressants (codeine, dextrometorphan, pholcodine, noscapine) given in isolation have a better efficacy/adverse effects ratio and are normally used in this indication.

### **4.3. Transparency Committee recommendations**

The transparency Committee recommends maintaining inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 15%