TRANSPARENCY COMMITTEE

OPINION

10 December 2008

CIRCADIN 2 mg prolonged-release tablet
PVC/PE/PCTFE blister pack(s) containing 21 tablets (CIP: 384 141-5)

Applicant: LUNDBECK

Melatonin

ATC Code: N05CH01

List I

Date of marketing authorisation (centralised procedure): 29 June 2007

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

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Melatonin

1.2. Indication

"Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over."

1.3. Dosage

Oral use. Tablets should be swallowed whole.
The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food. This dosage should be continued for three weeks.

*Paediatric use*
Circadin is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

*Renal impairment*
The effect of any stage of renal insufficiency on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to such patients.

*Hepatic impairment*
There is no experience of the use of Circadin in patients with liver impairment. Published data demonstrate markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, Circadin is not recommended for use in patients with hepatic impairment.

1.4. Pharmacodynamic properties

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and the light-dark cycle regulation. It is also associated with a hypnotic effect and increased propensity for sleep.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

N  Nervous system
05  Psycholeptics
C  Hypnotics and sedatives
H  Melatonin receptor agonists
01  Melatonin
2.2. Medicines in the same therapeutic category

In France, melatonin-based preparations are made up by pharmacists and prescribed off-label.

Melatonin-based preparations (1-5 mg) in the form of nutritional supplements are freely available in many countries.

2.3. Treatments with a similar therapeutic aim

2.3.1 Symptomatic drug treatments

Hypnotics

Medicinal products indicated for severe sleep disorders in occasional insomnia and transient insomnia

Benzodiazepines (BZD):
- Loprazolam: HAVLANE® 1 mg, scored tablet (B/20)
- Lorazepam: NOCTAMIDE® 1 mg and 2 mg, scored tablet (pack of 14)
- Temazepam: NORMISON® 10 mg (B/14), 20 mg (B/7) tablet
- Nitrazepam: MOGADON® 5 mg, scored tablet (B/20, B/100)
- Estazolam: NUPTALON® 2 mg, tablet (B/20)
- Flunitrazepam: ROHYPNOL® 1 mg, film-coated scored tablet (B/7, B/100)

Related to BZD:
- Zolpidem: STILNOX® 10 mg, film-coated scored tablet (B/7, B/14) and generics
- Zopiclone: IMOVANE® 3.75 mg film-coated tablet (B/5, B/14) and IMOVANE® 7.5 mg, film-coated scored tablet (B/5, B/14) and generics

Medicinal products indicated for insomnia, occasional insomnia and transient insomnia or severe sleep disorders in occasional insomnia and transient insomnia

H1 Antihistamines

- Doxylamine: DONORMYL 15 mg, film-coated scored tablet and effervescent tablet (tubes of 10 tablets) (Not reimbursed)
- Meprobamate + acepromazine: MPRONIZINE®, coated scored tablet (B/30)
- Chlorazepate + acepromazine: NOCTRAN®, scored tablet (B/30)
- Alimemazine: THERALENE® 5 mg, film-coated scored tablet (bottle/50 tablets), syrup (bottle of 150 mL) and oral solution (drops) 4% (bottle/30 mL)
- Promethazine: PHENERGAN® 25 mg, coated tablet (B/20)

Phytotherapy medicines

Medicinal product traditionally used for symptomatic treatment of neurotonic conditions in adults and children, particularly for minor sleeping problems.
Proprietary products based on hawthorn and/or passion flower and/or valerian. None of these products is reimbursed.
2.3.2 Non-drug treatments

- Sleep hygiene advice
- Relaxation methods
- Chronobiological methods
- Stimulus control
- Restriction of time spent in bed

Cognitive and behavioural therapies, combining sleep hygiene advice, stimulus control, restriction of sleep time and relaxation methods.
- Light therapy

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy data

The registration dossier includes the results of five randomised placebo-controlled efficacy studies. The results of the NEURIM I (CIRCADIN 2 mg, 40 patients), NEURIM IV (CIRCADIN 0.2, 0.5 and 2 mg, 263 patients) and NEURIM V (CIRCADIN 1, 2 and 5 mg, 393 patients) studies were inconclusive; the data from the two dosage studies were not sufficient to determine the dose to be studied in phase III.

The two randomised, double-blind, parallel-group phase III studies (NEURIM VII\(^1\) and NEURIM IX\(^2\)) evaluated the efficacy of prolonged-release melatonin at a dose of 2 mg per day for 3 weeks versus placebo in outpatients aged 55 or over with a diagnosis of primary insomnia according to the DSM-IV\(^3\) criteria (see section 4.3) made at least one month previously.

Patients whose mean sleep quality score on the LSEQ questionnaire\(^4,5,6,7\) was less than or equal to 40 mm, after a pre-inclusion period of two weeks on placebo, were not included. Treatment with a psychotropic drug within the 2 weeks prior to the start of NEURIM VII, within 3 months of the start of NEURIM IX and use of a hypnotic or any treatment used as a hypnotic during the pre-inclusion period were criteria for non-inclusion.

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1 Lemoine et al. Prolonged release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J. Sleep Res. 2007; 16:372–380.
NEURIM VII study

The primary endpoint was change from baseline in mean QOS (quality of sleep) score on the LSEQ questionnaire, measured over the last three consecutive nights of the 3-week treatment period. A score of 50 mm corresponds to "No change".

Of the secondary endpoints, the sleep diary parameters\(^1\) (QON, QOD) were evaluated. Symptoms occurring at the end of the treatment period were collated using the BWSQ questionnaire\(^2\).

One hundred and eighty eight patients, with a mean age of 68.5 years, were randomised into a three-week double-blind period to receive either prolonged-release melatonin (n=94) or placebo (n=94). Six patients stopped taking the treatment (melatonin 4, placebo 2).

Eighteen patients were excluded from the ITT analysis.

On inclusion, mean QOS scores for patients analysed was 65 mm; mean BFW, GTS and AFS scores were between 57 and 61 mm.

Change in scores from baseline (mm):

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Melatonin SR 2 mg n=82</th>
<th>Placebo n=88</th>
<th>Diff. versus placebo 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSEQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOS</td>
<td>-22.5 (20.7)</td>
<td>-16.5 (17.8)</td>
<td>-5.97 (-11.87; -0.08)</td>
<td>0.047</td>
</tr>
<tr>
<td>BFW</td>
<td>-15.7 (20.2)</td>
<td>-6.8 (16.0)</td>
<td>-8.87 (-14.45; -3.29)</td>
<td>0.002</td>
</tr>
<tr>
<td>GTS</td>
<td>-14.5 (19.1)</td>
<td>-14.2 (17.2)</td>
<td>-0.37 (-5.98; 5.22)</td>
<td>ns</td>
</tr>
<tr>
<td>AFS</td>
<td>-15.2 (21.4)</td>
<td>-10.2 (18.5)</td>
<td>-5.07 (-11.2; 1.06)</td>
<td>ns</td>
</tr>
<tr>
<td>Sleep diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QON</td>
<td>0.89 (0.78)</td>
<td>0.46 (0.97)</td>
<td>0.42 (0.14; 0.70)</td>
<td>0.003</td>
</tr>
<tr>
<td>QOD</td>
<td>0.42 (0.66)</td>
<td>0.27 (0.67)</td>
<td>0.15 (-0.06; 0.36)</td>
<td>ns</td>
</tr>
<tr>
<td>BWSQ (new symptoms)</td>
<td>29% (n=94)</td>
<td>29% (n=93)</td>
<td>-</td>
<td>ns</td>
</tr>
</tbody>
</table>

QOS = Quality Of Sleep (Questions 4,5), BFW = Behaviour Following Wakening (Questions 8-10), GTS = Getting To Sleep (Questions 1-3), AFS = Awakening From Sleep (Questions 6,7).

1 QON = quality of night, QOD = quality of day, scale from 0 (very bad) to 5 (very good).

NEURIM IX study

The primary efficacy endpoint was percentage of responders, defined as those experiencing improvement in quality of sleep (QOS) and behaviour following wakening (BFW) of more than 10 mm after 3 weeks of treatment. Of the secondary endpoints, the PSQI\(^1,2\) and QON and QOD parameters of the sleep diary were evaluated.

Of the 523 pre-included (including 99 who responded to placebo), 354 patients, with a mean age of 66 years, were randomised into a three-week double-blind period to receive either prolonged-release melatonin (n=177) or placebo (n=177). 20 patients stopped taking the treatment: 8 patients in the prolonged-release melatonin arm versus 12 in the placebo arm.

Data from 334 patients were analysed: prolonged-release melatonin (n=169) and placebo (n=165). On inclusion, mean QOS, BFW, GTS and AFS scores were between 52 and 54 mm. Mean initial PSQI scores were 11.

Change in scores from baseline (mm):

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Melatonin SR 2 mg</th>
<th>Placebo</th>
<th>Diff. versus placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=169</td>
<td>N = 165</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>LSEQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOS</td>
<td>-8.6 (16.3)</td>
<td>-4.2 (14.7)</td>
<td>-4.0 (-7.2; -0.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>BFW</td>
<td>-7.0 (14.1)</td>
<td>-4.1 (13.9)</td>
<td>-3.0 (-5.9; -0.2)</td>
<td>0.038</td>
</tr>
<tr>
<td>GTS</td>
<td>-7.3 (13.3)</td>
<td>-3.6 (11.3)</td>
<td>-3.7 (-5.8; -0.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>AFS</td>
<td>-4.5 (13.4)</td>
<td>-2.9 (14.3)</td>
<td>-2.0 (-4.8; 0.8)</td>
<td>ns</td>
</tr>
<tr>
<td>PSQI</td>
<td>-2.5 (3.3)</td>
<td>-1.8 (3.3)</td>
<td>-0.6 (-1.3; 0.1)</td>
<td>ns</td>
</tr>
</tbody>
</table>

QOS = Quality Of Sleep (Questions 4,5), BFW = Behaviour Following Wakening (Questions 8-10), GTS = Getting To Sleep (Questions 1-3), AFS = Awakening From Sleep (Questions 6,7).

Changes in QON and QOD scores in the sleep diary did not differ from those observed for placebo.

3.2. Safety data

The number of patients exposed to CIRCADIN in the context of clinical trials is estimated to be 1361. Three hundred and sixty three patients received the treatment for 6 months, and 146 for at least a year. The first regular pharmacovigilance report on CIRCADIN (29/06/2007 - 28/12/2007) estimated that exposure to the product was 512 patient-years. There were no reported spontaneous reports of adverse effects.

In these trials, with a 3-week treatment period, adverse effects were no more frequent for prolonged-release melatonin than for placebo (37% versus 32%). The most commonly observed adverse effects (> 3%) were: headache, pharyngitis, back pain and asthenia. Nineteen serious events were reported, including 3 deaths of patients receiving CIRCADIN: 13 in patients on prolonged-release melatonin, 6 in patients on placebo. These events were...


The PSQI is a self-rated questionnaire resulting in a global score between 0 and 21, which assesses sleep quality and disturbances over 1-month time interval. It consists of seven subscores: Sleep quality, Sleep onset latency, Sleep duration, Sleep efficiency, Sleep disturbances, Use of sleeping medication, Daytime dysfunction. Higher score indicates worse sleep quality.

not considered to be treatment-linked. Sixteen patients on prolonged-release melatonin (1.3%) and 42 patients receiving placebo stopped treatment because of adverse events. The frequency of adverse events did not increase at the end of the treatment. Percentage of symptoms evaluated using the Tyrer questionnaire (BWSQ) was not increased at the end of the treatment.

3.3. Conclusion

The two phase III clinical studies submitted to CHMP in 2005 showed that CIRCADIN had modest effect size when administered for 3 weeks at a fixed dose of 2 mg/day in terms of quality of sleep and behaviour following wakening, as measured by the QOS and BFW scores on the LSEQ questionnaire in outpatients aged over 55 with primary insomnia. The severity of insomnia of patients in NEURIM VII was not specified.

Mean variation in QOS score was greater for prolonged-release melatonin than for placebo (difference between treatments -4 and -6 mm). Mean variation in BFW score was greater for prolonged-release melatonin than for placebo (difference between treatments -3 and -9 mm). These variations in scores on a scale from -50 to +50 mm are modest, and of limited clinical relevance.

An improvement of less than 10 mm in the QOS and BFW score was observed in 26% of patients receiving prolonged-release melatonin versus 15% of those receiving placebo in NEURIM IX and in 47% versus 27% in NEURIM VII.

Data analysis showed no difference in variation in AFS scores (concerning quality of awakening) between the two arms. Only NEURIM IX showed a very modest difference in variation in the getting to sleep score (GTS = 3.3 mm) versus placebo.

These sleep parameters reverted towards baseline scores after treatment stopped.

Clinical data concerning CIRCADIN suggest a favourable efficacy/safety ratio in the short term. However, clinical results obtained with CIRCADIN are not relevant to the geriatric population aged over 65 who have multiple pathologies or who are very old, and who often take multiple medications.

The risk of drug interactions, either pharmacokinetic (metabolism of cytochrome P450 in the liver (CYP1A1/1A2)) or pharmacodynamic, in particular with other psychotropic drugs, could limit its use. Caution should be used when melatonin is administered to patients with renal impairment. CIRCADIN is not recommended for patients with hepatic impairment. However, no withdrawal or rebound effect has been observed during product development. The European Risk Management Plan includes one study that evaluates symptoms that occur when CIRCADIN treatment is discontinued.

It has not been established whether prolonged-release melatonin has sustained efficacy in chronic insomnia; there are no efficacy data from controlled studies for treatment period of more than 3 weeks.

The Committee regrets that there are no direct comparative studies versus active drug or non-drug treatments.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

Sleep disturbance and the associated daytime repercussions can have harmful consequences on overall function and can lead to the onset or worsening of physical or psychological conditions.

This product provides symptomatic treatment for primary insomnia.

The efficacy/adverse reactions ratio for this medicinal product is modest.

Alternative medicinal and non-medicinal products exist.

Public Health Benefit:

Primary insomnia is a significant public health burden. The burden can be considered as moderate in this indication, because of the more limited number of patients affected (patients aged 55 or over) in comparison with the total number of patients with primary insomnia.

Improvement of the sleep of patients with insomnia and a reduction in overconsumption of benzodiazepines and related substances are public health needs. Attempts to meet these needs should not be limited to a drug-based approach (and should include e.g. training of prescribers, patient education, non-drug approaches).

The expected impact of prolonged-release melatonin in terms of improvement in quality of life and reduction in morbidity linked to insomnia cannot be quantified, in particular because of the lack of direct comparison with available treatments.

It is not certain that results can be transposed into general practice, given the practical difficulty of diagnosing primary insomnia, and the lack of data concerning the severity of insomnia.

Questions arise as to whether a short-term treatment for chronic insomnia is useful, and as to how patients should be managed after they stop taking this treatment. CIRCADIN could provide a partial response to the public health need, by enabling a reduction in the overconsumption of benzodiazepines and related substances and the iatrogeny associated with this.

However, given the currently available data, CIRCADIN is not useful in a public health context. It is regrettable that there are no data concerning the possible savings in the use of benzodiazepines and related substances, which could be of benefit to public health.

The actual benefit of this proprietary drug is low. This actual benefit is granted for 18 months, and is conditional. It is conditional on an assessment of the impact of CIRCADIN use on the consumption of hypnotics such as benzodiazepines or related substances in France; it will be re-assessed 18 months after inclusion on the list of medicines reimbursed by National Insurance, in view of the results of the follow-up study requested by the Committee (see paragraph 4.5). It will be re-assessed if a product with a higher efficacy/safety ratio in the treatment of insomnia is included on the list of medicines reimbursed by National Insurance.
4.2. Improvement in actual benefit

Given the weakness of the clinical efficacy data that have been presented, the Transparency Committee considers that CIRCADIN does not provide any improvement in actual benefit in the management of primary insomnia.

4.3. Therapeutic use

Various categories of insomnia have been identified and classified according to chronic nature or presumed aetiology of sleep problems (DSM-IV, ICSD-2).

"Primary insomnia, as defined in DSM-IV, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance does not occur exclusively during the course of another sleep disorder or of a mental disorder, and is not due to the direct physiological effects of a substance or a general medical condition." This definition includes some diagnoses in the ICSD-2 classification, such as psychophysiological insomnia, sleep state misperception, idiopathic insomnia, and some cases of inadequate sleep hygiene.

Investigations for secondary or comorbid insomnia that is linked to a physical or psychological pathology, to a circadian rhythm disturbance, to toxicity and/or environmental factors (e.g. alcohol, coffee, tobacco, other stimulants, medications, noise) must have returned negative results.

With increasing age comes a considerable increase in complaints of insomnia. In elderly patients, three specific features can be observed: polyphasic sleep, advanced phase and flattened circadian rhythms. Early rising and early sleeping are normal. Periods of wakefulness between sleep increase in number and duration. The sleep effectiveness index is reduced. Daytime sleep occurs in increasingly frequent and lengthy naps.

A meta-analysis concerning objective sleep parameters in good sleepers showed that sleep onset latency increased with age, that total duration of sleep reduced and that periods of wakefulness between sleep increased.

The patient should be made aware of these ideas, in order to dissuade him/her from starting on ill-advised courses of treatment.

In all cases of insomnia, it is useful to ensure that the patient has properly understood and is prepared to observe the essential rules of sleep hygiene, in terms of bedtime and getting up schedules, environmental factors (noise, light, temperature), time spent in bed, physical activity, taking stimulants at the wrong time.

If hypnotics are prescribed, this must be part of a short-term strategy. A strategy for stopping these treatments must be established from the start, with the patient’s co-operation. Treatment with benzodiazepines or related substances, which are indicated in the treatment of severe sleeping problems in the context of occasional insomnia or transient insomnia are generally prescribed in chronic insomnia, and in most cases are taken for prolonged periods. These treatments can have residual effects, in terms of memory problems and changes in cognitive functions. The risk/benefit ratio in elderly patients has been discussed, particularly in terms of prolonged courses of treatment (off-label) which are made more likely by

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2 Report on sleep. Ministry of Health and Solidarity (France). December 2006
substance dependence. Antihistamine sedatives are not recommended for elderly patients. The indication for CIRCADIN is limited to primary insomnia in patients aged over 55. Phytotherapy can be used to relieve minor sleep problems.

Non-drug techniques are not well-developed in France, and are therefore relatively inaccessible. They are particularly indicated for chronic insomnia (primary or secondary) but can 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 methods, chronobiology, stimulus control and sleep restriction.

Cognitive and behavioural therapies that combine these approaches are broadly recommended by experts for the treatment of chronic insomnia, particularly primary insomnia.

Some circadian rhythm disorders in elderly patients are likely to improve with light therapy.

Referral to a specialist is required in some specific cases:
- insomnia that has failed to respond to properly-administered treatment;
- suspected physical cause requiring sleep study (restless legs syndrome, periodic limb movement disorder, respiratory problems or heart rhythm disorders during sleep);
- chronic unexplained insomnia, which is atypical or particularly complex, with significant daytime repercussions.

4.4. Target Population

Epidemiological studies of sleep disorders have revealed major disparities in prevalence of insomnia.

In the study by Léger\(^1\) that was carried out in France in 1997, involving 12,778 people aged 18 and over, the prevalence of insomnia (at least one of the following 4 complaints: difficulties falling asleep, waking during the night, waking too early, unrefreshing sleep) at least three nights per week over at least one month, accompanied by daytime repercussions (the DSM-IV criteria for insomnia) was observed in 19% of cases. In the 50-65 and over-65 age groups, the percentage was 20%.

Severe insomnia (at least 2 of the above complaints, with daytime repercussions) was observed in 9% of people (11.6% in the 50-65 age group and 12.5% in the over-65s).

According to data from the Ohayon study\(^2\) which was carried out in France in 1993 and which involved 5622 people aged 15 and over, the prevalence of insomnia (complaints such as difficulties in getting to sleep and/or staying asleep, waking too early, unrefreshing or poor quality sleep accompanied by dissatisfaction linked to sleeping problems or use of a hypnotic treatment was 18.6%. Primary insomnia (DSM-IV) was observed in 73 people (22% were aged over 65, 33% between 45 and 64).

On 1 January 2008, the population of mainland France and its overseas territories aged over 15 was estimated to be 51.9 million. According to the study by Ohayon, the prevalence of primary insomnia in the general population is 1.3%, giving around 670,000 people. If the subpopulation of over-55s is estimated to be 40% of this population, the number of people likely to be able to receive treatment with prolonged-release melatonin for primary insomnia is around 270,000. This estimate of the target population is drawn from epidemiological data based on the DSM-IV criteria, and it is not certain whether these can be transposed into real life.

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4.5. Transparency Committee recommendations

The Transparency Committee approves 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 for the indication (patients over 55) and at the dosages given in the marketing authorisation, for a duration of 18 months.

Given the conditional actual clinical benefit attributed to CIRCADIN, the Transparency Committee wishes to see further data in order to evaluate the impact of CIRCADIN use on the consumption of hypnotics such as benzodiazepines or related substances in France and in particular 18-month follow-up data from reimbursements by CNAMTS (French National Health Insurance Fund) and sales of hypnotics, particularly CIRCADIN. Co-prescription of these medicinal products, as well as need for use of a benzodiazepine or related substance immediately following prescription of CIRCADIN will also be counted. Data provided by the applicant will be considered.

In addition, the Transparency Committee wishes a follow-up study involving patients treated with CIRCADIN, which would determine:

- characteristics of patients treated (e.g. sex, age, type and severity of insomnia);
- actual conditions under which CIRCADIN is used (in particular dosage, duration of treatment, prior treatments, concomitant treatments);
- the impact of CIRCADIN on care pathways for patients in the context of insomnia (e.g. prescription of benzodiazepines and related substances, non-drug approaches). The duration of patient follow-up shall be determined by an independent scientific committee.

If planned or current studies, particularly under the European Risk Management Plan, do not answer all the questions posed by the Transparency Committee, a specific study will have to be carried out. Analysis of the protocol will be carried out in conjunction with Afssaps with respect to the relevant objectives.

4.5.1 Packaging

The packaging is appropriate for the prescribing conditions laid down in the marketing authorisation (one tablet per day for three weeks). The Committee wishes to draw attention to the fact that the prescription duration for CIRCADIN is 21 days and not 28 or 30 days.

4.5.2 Reimbursement rate: 35%