Review of the dossier of the proprietary drug(s) included on the list for a period of 5 years as from 21 January 2005 (Official Gazette of 3 November 2005)

Celance 0.05 mg, scored tablet
B/30 (CIP code: 338 081-3)

Celance 0.25 mg, scored tablet
B/30 (CIP code: 338 084-2)

Celance 1 mg, scored tablet
B/90 (CIP code: 338 086-5)

Applicant: Lilly France SA

Pergolide (mesilate)
ATC code: N04BC02

List I
Initial prescription by neurologists only
Medicine requiring special monitoring during treatment

- 05/08/2003 - addition of the risk of cardiac valve disease to the risk of fibroses in the sections dealing with warnings, precautions for use and adverse effects.
- 24/09/2004 - updating of contraindications and drug interactions relating to the combination with phenylpropanolamine.
- 14/12/2004 - amendments relating to fibrous damage: restriction of the indications “in the event of failure of other dopamine agonist treatments” and of the conditions of prescription (initial prescription by neurologists only), addition of a maximum recommended dose and of contraindications in patients with a history of fibrosis or suffering from cardiac valve disease confirmed by anatomical examination, strengthening of recommendations on clinical monitoring and the performance of echographs on patients.
- 21/05/2007 - addition of pathological gambling and hypersexuality to the adverse effects.
- 23/02/2009 - maximum dose reduced to 3 mg/day, reference to cardiac valve diseases and associated disorders as very common adverse effects, and changes to the wording of special warnings and precautions for use regarding the risk of fibrosis and valve disease.

Reason for request: Request for renewal of inclusion on the list of medicines refundable by National Health Insurance.

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

1.1. Active ingredient

Pergolide (rye ergot derivatives)

1.2. Indications

“Treatment of Parkinson’s disease.

If treatment with a dopamine agonist is being considered, pergolide is indicated as second-line therapy in patients who fail treatment with other dopamine agonist treatments, as monotherapy, or as adjunctive treatment with levodopa in the management of the signs and symptoms of Parkinson’s disease.

Treatment should be initiated under specialist supervision (neurologist). The benefit of continued treatment should be regularly reassessed, taking into account the risk of fibrotic reactions and valve disease (see sections headed ‘Contraindications’, ‘Special warnings and precautions for use’ and ‘Adverse effects’).

Pergolide is used:

- As monotherapy, to postpone dopa therapy and its motor complications, particularly various forms of dyskinesia.

- In combination with levodopa when motor complications of dopa therapy occur, i.e.:
  - fluctuations in the therapeutic effect (end-of-dose deterioration, on-off effect, nocturnal akinesia).
  - all types of abnormal involuntary movements (“mid-dose”, diphasic, dystonic, whether or not associated with pain).

Combining pergolide with levodopa must always be conducted gradually, with the option to reduce levodopa doses (see section headed ‘Dosage and method of administration’).”

1.3. Dosage

“Pergolide treatment must be introduced gradually and in stages, aiming to find the lowest effective dosage. The optimum daily dosage will vary from one individual to another on the basis of efficacy and tolerance.

The average effective dosages of pergolide are generally 1 to 3 mg daily (ranging from 0.75 to 3 mg per day).

The maximum dose of 3 mg daily must not be exceeded.

As the therapeutic index is less favourable in elderly patients, a lower dosage of around 1 to 2 mg daily is recommended.” […]

1.4. Contraindications

“This medicine must never be prescribed in the following cases:

- To patients who are hypersensitive to pergolide mesilate or other rye ergot derivatives.

- To patients with a history of fibrosis.

- To patients suffering from cardiac valve disease confirmed by anatomical examination, irrespective of which valve(s) is/are involved (e.g. echocardiography showing a thickening of the valve wall, stenosis, or mixed valvular damage with insufficiency and stenosis).

- In combination with phenylpropanolamine.

- In combination with anti-emetic neuroleptics.”
1.5. Special warnings and precautions for use

[...]

"Fibrosis and cardiac valve disease and possibly related clinical phenomena:
Fibrotic and serosal inflammatory disorders, such as pleurisy, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valve disease involving one or more valves (aortic, mitral and tricuspid), or retroperitoneal fibrosis, have occurred after prolonged usage of rye ergot derivatives with agonist activity at the serotonin 5HT2B receptor, such as pergolide. In some cases, symptoms or manifestations of cardiac valve disease improved after discontinuation of pergolide.

There is evidence that higher doses and/or cumulative exposure are risk factors for development of valvular disease. However, valve disease and fibrotic reactions have been reported during treatment with pergolide at doses less than 0.5 mg/day.

**Before starting treatment:**
All patients must undergo a cardiovascular assessment, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory lung function/chest X-ray and renal function prior to initiation of therapy.

In patients with valvular regurgitation, it is not known whether pergolide treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with pergolide.

**During treatment:**
Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis.

Therefore, during treatment attention should be paid to the signs and symptoms of:
- pleuro-pulmonary disease: dyspnoea, shortness of breath, persistent cough or chest pain;
- renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the kidneys/flanks and lower limb oedema, as well as any abdominal masses or tenderness that may indicate retroperitoneal fibrosis;
- cardiac failure; observed cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disorders is essential. Following treatment initiation, the first echocardiogram must be carried out within 3 to 6 months; thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment, with particular emphasis on the aforementioned signs and symptoms, but in all cases an echocardiogram must be carried out at least every 6 to 12 months.

Pergolide should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening.

The need for other clinical monitoring (e.g. clinical examination, including cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.
Additional appropriate investigations such as erythrocyte sedimentation rate and serum creatinine measurement should be performed if necessary to support a diagnosis of a fibrotic disorder." [...]

3/9
2. REMINDER OF THE COMMITTEE’S OPINIONS AND CONDITIONS OF INCLUSION

Opinion relating to renewal of inclusion
20 July 2005

The actual benefit of pergolide in the new indication wording is low.

The Committee is of the opinion that CELANCE offers no improvement in actual benefit (IAB V) in the therapeutic management of Parkinson’s patients who have “failed” on other dopamine agonist treatments.

3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification

N Nervous system
N04 Anti-Parkinson drugs
N04B Dopamine agents
N04BC Other dopamine agents
N04BC02 Pergolide

3.2. Medicines in the same therapeutic category

Dopamine agonists:

Ergot derivatives
- bromocriptine: Parlodel tablet, capsule and generics
- lisuride: Dopergin, Arolac, scored tablets

Non-ergot substances
- piribedil: Trivastal, coated tablet
- pramipexole: Sifrol tablet and Sifrol prolonged-release tablet
- ropinirole: Requip tablet and Requip LP prolonged-release tablet

Other dopamine agonists:
- apomorphine: Apoklon, solution for injection
- rotigotine: Neupro, skin patch
4. UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION

4.1. Efficacy data

The dossier submitted does not include any new efficacy data.

A Cochrane review published in 2010\(^1\) assessed the efficacy and tolerance of adjuvant treatment to levodopa therapy in Parkinson’s disease patients with motor complications. The bibliographical search was conducted principally on the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE, EMBASE, PubMed, LILACS and Web of Science. This review looked at 44 randomised, double-blind, placebo-controlled trials (8,436 patients) which had assessed three classes of treatment given in conjunction with levodopa (dopamine agonist, COMT inhibitors and MAO-B inhibitors) in patients with Parkinson’s disease and motor complications. The mean duration of patient follow-up was 20 weeks. The patients had been suffering from Parkinson’s for nine years on average. Analysis of the data confirms that these anti-Parkinson’s drugs administered as add-on treatments reduce off time, allow levodopa to be given at lower doses and improve motor scores. However, there was an increased incidence of dyskinesia and other adverse effects such as constipation, hallucinations and vomiting. Indirect comparisons of these three classes of anti-Parkinson’s drugs suggest that dopamine agonists are more effective at controlling symptoms than COMT inhibitors and MAO-B inhibitors. The data available is insufficient to differentiate between the efficacy of individual dopamine agonists or between any other medicines in the same class.

4.2. Tolerance data

a. Reassessment of the risk of fibrosis and valve disease by the CHMP\(^2\)

At the request of the United Kingdom, the Committee for Medicinal Products for Human Use (CHMP) reassessed the risk of fibrosis and cardiac valve disease associated with the use of all dopamine agents derived from rye ergot. The review was carried out in June 2007. All the information available relating to this risk, obtained from clinical trials, observational studies and “spontaneous reports” of adverse effects made by patients or doctors to companies or the health authorities, were examined.

Spontaneous cases of fibrotic reactions were reported for all dopamine agonists derived from ergot, especially when they were administered at high doses and after long periods of treatment. Overall, data from the spontaneous reports indicates that the risk of fibrosis and valve disease is higher in patients taking cabergoline and pergolide than in those taking bromocriptine, lisuride or dihydroergocryptine. Most of the fibrotic events reported were not completely reversible, although symptoms sometimes improved for various reasons and the fibrosis did sometimes abate.


Four main observational studies were carried out to investigate the risk of cardiac valve disease in patients taking dopamine agonists for Parkinson's disease (Zanettini et al., NEJM, 2007; Schade et al., NEJM 2007; Yamamoto et al., Neurology 2006; Peralta et al., Movement Disorders 2006). The study carried out by Schade et al. found that the adjusted incidence rate ratio (IRR) for symptomatic valvular regurgitation was higher for cabergoline and pergolide than for bromocriptine, lisuride and the non-ergot-derived dopamine agonists pramipexole and ropirinole, for which no cases have been reported.

On the basis of the information available, the CHMP concluded in June 2008 that the marketing authorisations for ergot-derived dopamine agonists should be maintained, but that changes should be made to the SPCs for these medicines in order to reduce the risk of fibrosis. The CHMP also took the view that the risk of fibrosis, especially cardiac valve fibrosis, was not the same for all the five medicines in this class. The CHMP found that the risk of cardiac valve fibrosis was well established in the case of cabergoline and pergolide. It recommended that the SPCs of these two medicines be updated to include:
- a warning specifying the recommended approach to echocardiograph monitoring;
- a reduction in the maximum dosage to 3 mg per day;
- reference to cardiac fibrosis as a very common adverse effect.

b. National pharmacovigilance committee

Update on the use of pergolide and cases of cardiac valve disease reported in relation to the product

In September 2003, 18 cases of cardiac valve disease had been reported throughout the world among patients being treated with pergolide. One of these cases had occurred in France. Approximately 520,000 patients had been exposed to this drug, including 27-28,000 in France (Letter to prescribing physicians, September 2003). The Toulouse Regional Pharmacovigilance Centre was asked to conduct an official pharmacovigilance investigation into cases of valve disease reported in patients being treated with CELANCE, which was first placed on the French market in 2000.

As of 15 December 2004, 48 cases of cardiac valve disease in patients taking CELANCE had been reported in France. The number of patients exposed was estimated at 32,500 (Letter to prescribing physicians, January 2005). The benefit/risk ratio for pergolide was reassessed, leading to changes to the Summary of Product Characteristics with regard to indications, dosages, contraindications, warnings and precautions for use.

Updated information on this subject was presented to the members of the National Pharmacovigilance Committee in March 2007. As of February 2007, 103 cases of patients taking pergolide developing valve disease had been reported in France. A study conducted by the Midi-pyrénées health insurance fund found no evidence of misuse of the product. However, it was decided to set up a monitoring system in cooperation with the health insurance funds, allowing prescribing data for the product to be obtained and to confirm absence of misuse.

The National Pharmacovigilance Committee re-examined this issue in March 2009. Five observations linking pergolide and cardiac adverse effects had been reported to the regional pharmacovigilance network since February 2007. One case had been reported to the manufacturer (Lilly). Data from the Midi-Pyrénées (Toulouse), Pays de Loire (Nantes) and Nord Picardie (Amiens) regional health insurance funds had found misuse, with failure to comply with the requirement to prescribe the product as last-line treatment and failure to have echocardiograms performed at regular intervals as recommended in the SPC.
Attention was drawn to the sharp decline in the number of patients exposed to pergolide in France and the rest of Europe. The fact that a very small number of patients with Parkinson's disease obtain clinical benefit from this drug was pointed out again.

**Update on behavioural disorders related to levodopa and dopamine agonists**

The French health products tolerance agency, Afssaps, drew the attention of healthcare professionals to the risk of compulsive and repetitive behaviour (Letter to healthcare professionals, July 2009).

**4.3. Conclusion**

No difference in efficacy between the various dopamine agonists available was shown. The tolerance data confirm the by now well-established risk of fibrosis and cardiac valve disease attributable to pergolide. This risk is greater if patients do not undergo the echocardiograms recommended in the SPC.

### 5. DRUG USAGE DATA

These proprietary drugs are not sufficiently widely used in a community medicine setting to feature on the prescription panels available.

The data utilised comes from a Thalès community medicine prescription monitoring study conducted for the period 2007 to 2009 among a sample of 61 neurologists practising in the community. By extrapolating this data, the number of patients prescribed CELANCE once during this period can be estimated at 1,800. It is thought that the figure for 2009 would be slightly over 500.

### 6. TRANSPARENCY COMMITTEE CONCLUSIONS

**6.1. Re-assessment of actual benefit**

Parkinson's disease associates resting tremor, rigidity, bradykinesia or akinesia and loss of postural reflexes. As the disease progresses, neurovegetative disturbances, sensory painful complaints and mental disorders are associated with these motor disorders. The onset of Parkinson's disease is usually insidious with a slow and progressive clinical course characterised by a progression of disability over time and a marked reduction in quality of life. It is a life-threatening disease.

CELANCE is an anti-Parkinson's drug which aims to treat the symptoms. The efficacy/adverse effects ratio for CELANCE is modest at best.

CELANCE is the only dopamine agonist indicated after failure of other dopamine agonists, because of the by now well-established risk of fibrosis and of cardiac valve disease in particular. Many other dopamine agonists are indicated for Parkinson's disease, and in particular there are a number of non-ergot agonists available.

**Public health benefit:**

Parkinson's disease represents a considerable public health burden. The public health burden in the very small sub-population of Parkinson's patients for whom the proprietary drug CELANCE may be indicated is low.
Delaying the onset of severe functional limitations for patients is a public health objective (law of 9 August 2004 on public health policy). To date, the proprietary drug CELANCE has no population impact in view of the lack of efficacy data for patients who have failed other dopamine agonist treatments and because of the serious adverse effects (fibrosis and valve disease). Consequently, CELANCE has no public health benefit.

The Committee considers that the actual benefit of the proprietary drug CELANCE compared to current treatments is now insufficient to be covered by National Health Insurance.

6.2. Therapeutic use 3, 4, 5, 6

Age at onset and degree of functional impairment are the two factors guiding the choice of therapy during the initial stage of the disease:

- In the absence of motor repercussions, treatment with medication is not absolutely vital
- where functional impairment is minimal, the prescribing physician has a choice of a dopamine agonist, an MAO-B inhibitor or an anticholinergic agent. The choice depends on the predominant symptom and the patient's age;
- when there is a more severe functional impairment, treatment depends on the patient's age:
  - in young subjects, dopamine agonists should be preferred for as long as possible. The use of dopa therapy is justified in the event of adverse effects or an insufficient therapeutic response. The dose of levodopa must remain as low as possible.
  - Levodopa may be used as first-line treatment in elderly subjects. The minimum effective dose should be used if the patient develops cognitive impairment.

After a “honeymoon” phase of good symptom control by treatment, the patient’s health status will worsen with the onset of dopa-induced motor disorders (motor fluctuations and dyskinesia) and the specific signs of the disease (dysautonomic cognitive impairment, psycho-behavioural signs) which are generally dopa-resistant.

Because of these motor complications caused by dopaminergic treatment, medicines should be sought that worsen the “off” periods and dyskinesia and dopa therapy should then be optimised (splitting the daily dose, adjusting the dosing schedule, prescribing different pharmaceutical forms).

The therapeutic management of these complications may also justify the combination of other drugs with levodopa:
- dopamine agonist
- COMT inhibitor
- MAO-B inhibitor (selegiline, rasagiline).

Rehabilitation plays a considerable role in the management of Parkinson's disease patients. Rehabilitation procedures must be adjusted, even in the short term, to the risks and fluctuations of the disease.

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3 Parkinson’s disease: diagnostic and therapeutic criteria. Consensus conference - 3 March 2000
Stereotactic surgery is an effective method of treatment for severe motor disorders in advanced Parkinson's disease and for intractable tremor.

6.3. Target population

CELANCE can be used in monotherapy in the initial phase of Parkinson's disease or in combination with levodopa at a later stage, when end-of-dose motor fluctuations occur. CELANCE is indicated in monotherapy or in combination in the event of failure of other dopamine agonists.

It is estimated that between 110,000 and 145,000 people have Parkinson's disease; 80 to 90% of these are treated with levodopa, in isolation in 30% of cases. This puts the number of patients whose condition is controlled by dopa therapy alone at between 26,000 and 40,000. Accordingly, the target population for dopamine agonists can be estimated at 84,000 to 105,000 patients. It is impossible to determine how many patients have failed on other dopamine agonists and might benefit from CELANCE.

Data from the pharmaceutical company indicates that in May 2010 fewer than 3,500 boxes a month were supplied, and less than 1% of the total were supplied to hospitals.

6.4. Transparency Committee recommendations

The transparency Committee does not recommend maintaining on the list of medicines refundable by National Health Insurance.

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