HAUTE AUTORITÉ DE SANTÉ

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

**TRANSPARENCY COMMITTEE**

**OPINION**

November 29, 2006

**EXELON 1.5 mg, capsule**
**bubble pack of 14 capsules, B/28 and B/56: cip 347 468-4 and 347 469-0**

**EXELON 3 mg, capsule**
**bubble pack of 14 capsules, B/28 and B/56: cip 347 471-5 and 347 472-1**

**EXELON 4.5 mg, capsule**
**bubble pack of 14 capsules, B/28 and B/56: cip 347 474-4 and 347 585-0**

**EXELON 6 mg, capsule**
**bubble pack of 14 capsules, B/28 and B/56: cip 347 587-3 and 347 589-6**

**EXELON 2 mg/ml, drinkable solution**
**Bottle of 50 ml: cip 363 489-2**

**Applicant: NOVARTIS Laboratory**

Rivastigmine (hydrogen tartrate)

List I
Initial annual prescription for use by doctors specialised in neurology or in psychiatry, by specialist doctors with a diploma in complementary specialised studies in geriatrics, and by specialist or general doctors qualified in gerontology.

Dates of the Marketing Authorisation Amendments (centralised procedure): May 12, 1998 (gel capsules), June 2, 1999 (oral solution), June 30, 2003, February 28, 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 of “Symptomatic Treatment of Mild to Moderately Severe Forms of Dementia in Patients with Idiopathic Parkinson’s Disease.”

# 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active Ingredient

Rivastigmine

## 1.2. Background

First medicinal product indicated for the symptomatic treatment of slight to moderately severe forms of dementia in patients with idiopathic Parkinson's disease.

## 1.3. Indications

Symptomatic treatment of slight to moderately severe forms of Alzheimer's disease.

First medicinal product indicated for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

## 1.4. Dosage

Method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia or dementia associated with Parkinson's disease. Diagnosis should be made according to current guidelines. Therapy with rivastigmine should only be started if a caregiver is available who will regularly monitor intake of the medicinal product by the patient.

Rivastigmine should be administered twice a day, with morning and evening meals.
The capsules should be swallowed whole.

Initial dose

1.5 mg twice a day.

Dose titration

The starting dose is 1.5 mg twice a day. If this dose is well tolerated after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. Subsequent increases to 4.5 mg and then 6 mg twice a day should also be based on good tolerability of the current dose and may be considered after a minimum of two weeks of treatment at that dose level.

Adverse reactions (e.g. nausea, vomiting, abdominal pain or loss of appetite, weight decrease or worsening of extrapyramidal symptoms (e.g. tremor)) in patients with dementia associated with Parkinson's disease may occur during treatment. These effects may regress by omitting one or more doses. If the adverse reactions persist, the daily dose should be reduced to the previous well-tolerated dose or the treatment may be discontinued.

Maintenance dose

The effective dose is 3 to 6 mg twice a day. To achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose. The recommended maximum daily dose is 6 mg twice a day.

Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of rivastigmine should be reassessed on a regular basis, especially for patients treated at doses less than 3 mg twice a day. If after 3 months of maintenance treatment the patient's rate of decline in dementia symptoms is not favourably altered, the treatment should be discontinued. The treatment should also be discontinued when evidence of a therapeutic effect is no longer present.

Individual response to rivastigmine is unpredictable. However, a greater treatment effect was seen in Parkinson's disease patients with moderate dementia. Similarly a greater effect was observed in Parkinson's disease patients with visual hallucinations.

Treatment effect has not been studied in placebo-controlled trials beyond 6 months.

Re-initiation of therapy

If treatment is interrupted for more than several days, it should be re-initiated at 1.5 mg twice daily. Dose titration should then be carried out as described above.

Renal and hepatic impairment
Due to increased exposure in moderate renal and mild to moderate hepatic impairment, dosing recommendations to titrate according to individual tolerability should be strictly followed (see section 5.2).
Patients with severe liver impairment have not been studied.

Children
Rivastigmine is not recommended for use in children.

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2006)

N Nervous system
06 Psychoanaleptics
D Dementia medicines
A Anticholinesterasics
03 Rivastigmine

### 2.2. Medicines in the same therapeutic category

Exelon is the only acetylcholinesterase inhibitor to have obtained this indication.

### 2.3. Medicines with a similar therapeutic aim

None

## 3. ANALYSIS OF THE AVAILABLE DATA

### 3.1. Efficacy

The file submitted comprises the results of the pivotal placebo controlled comparative study of patients with a dementia associated with Parkinson's disease.

An exploratory study conducted by the University Centres from the French pivotal assessed 28 patients using the Mattis scale, which is the best instrument for the diagnosis and monitoring dementias associated with Parkinson's disease.

#### 3.1.1 Pivotal Rivastigmine *versus* Placebo Study

*Emre M. et al. Rivastigmine for Dementia associated with Parkinson's Disease. N Engl J Med 2004;351:2509-18.*

*Poewe W. et al. Long-term Benefits of Rivastigmine in Dementia associated with Parkinson's Disease: an Active Treatment Extension Study. Movement Disorders 2006;21(4):456-61.*

ENA713B2311, a randomised double-blind study, compared the efficacy of and tolerance to rivastigmine 3 to 12 mg/d to those of the placebo in patients with idiopathic Parkinson's disease in accordance with UK PDSBB[1] criteria and a dementia caused by this disease in accordance with DSM-IV[2] (code 294.1) criteria whose symptoms appeared at least 2 years after Parkinson's disease had been diagnosed. The MMSE[3] score on inclusion ranged from 10 to 24.

The initial dosage was 1.5 mg twice daily; this was increased in increments of 3 mg daily at intervals of at least 4 weeks during a 16-week titration period.

The principal evaluation criteria of efficacy were variations in the total ADAS-cog[4] score (superiority threshold 2.25) the ADCS-CGIC[5] score (superiority threshold 0.4) at 24 weeks of treatment.

Among the secondary criteria, variations in the ADCS-ADL[6] and NPI-10[7] scores were also evaluated by comparison with the initial condition.

541 patients with an average age of 73 (87% ≥65) were randomised (ratio 2:1): rivastigmine (n=362), placebo (n=179).

The average age of Parkinson's disease was 9 years, that of the diagnosis of dementia approximately one year. Over 80% of the patients had a Hoehn and Yahr stage of 1 to 3. The initial average UPDRS[8] motor score (Part III) was 33.

***95% of the patients were receiving levodopa, and 46% dopaminergic agonists. Of the concomitant treatments, the patients were receiving a neuroleptic type benzodiazepine (27% of patients), a benzodiazepine (19% of patients in the rivastigmine group* vs *14% of patients in the placebo group), an ISRS (18% rivastigmine* vs *15% placebo), an other antidepressant (11% rivastigmine* vs *8% placebo).***

A dopaminergic treatment was introduced or adapted (dosage increased) for 17% of the patients under rivastigmine and 14% of the patients under placebo.

An antipsychotic treatment was introduced or adapted (dosage increased) for 10% of the patients under rivastigmine and15% of the patients under placebo.

The initial average MMSE score was 19. 76% of the patients showed a mild dementia (18≤MMSE≤24).

The average dosage of rivastigmine was 8.6 mg/d.

1 United Kingdom Parkinson's Disease Society Brain Bank (Queen Square Brain Bank)

2 Diagnostic and Statistical Manuel of Mental Disorders, 4th ed.

3 Mini-Mental State Examination (scored from 0 to 30) - Evaluation of Cognition. A high score indicates a better cognitive performance. Folstein M, Journal of Psychiatric Research 1975.

4 Alzheimer's Disease Assessment Scale - Cognitive Subscale (scored from 0 à 70) – Evaluation of Cognitive Functions (memory, orientation, language, visuospatial gnosias, praxias). High scores indicate a more serious condition. Rosen WG, Am J Psychiatry 1984.

5 Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change - 7 points (1=marked improvement, 7=marked deterioration). Schneider LS, Alzheimer Dis Assoc Disord 1997.

6 Alzheimer's disease Cooperative Study-Activities of daily living (score de 0 à 78) - Évaluation des activités de la vie quotidienne – High scores indicate a better performance. Galasko D, Alzheimer Dis Assoc Disord 1997.

7 Neuropsychiatric Inventory – Psychobehavioural Evaluation (10-ttem scale, scored from 0 to 120). A high score indicates greater behavioural disturbance. Cummings JL, Neurology 1994

8 UPDRS : Part I, Mentation, Behaviour and Mood (0-16) ; Part II, Activities of Daily Living (0-52); Part III, Motor examination (0-108); Part IV, Complication of therapy (0-23). Total score 0-199: 199 represents the worst disability, 0 represents no disability. Fahn S, Recent Developments in Parkinson's Disease, vol 2. Florham Park, NJ : Macmillan Health Care Information 1987.

Efficacy Data

Score variations after 24 weeks of treatment compared with the initial values
(ITT+RDO population: n=335 rivastigmine, n=166 placebo)

| Treatment | N | Av. Initial Value | Var. at 24 wks.[†] | Difference *vs* PL[††] (IC 95%) | p |
|---|---|---|---|---|---|
| ADAS-Cog | | | | | |
| Rivastigmine | 329 | 23.8 ± 10.2 | -2.1 ± 8.2 | 2.88 (1.44 ; 4.31) | < 0.001 |
| Placebo | 161 | 24.3 ± 10.5 | 0.7 ± 7.5 | - | |
| ADCS-CGIC | | | | | |
| Rivastigmine | 329 | - | 3.8 ± 1.4 | - | - |
| Placebo | 165 | - | 4.3 ± 1.5 | - | |
| ADCS-ADL | | | | | |
| Rivastigmine | 333 | 41.6 ± 18.6 | -1.1 ± 12.6 | 2.51 (0.35 ; 4.67) | 0.023 |
| Placebo | 165 | 41.2 ± 17.7 | -3.6 ± 10.3 | - | |
| NPI-10 | | | | | |
| Rivastigmine | 334 | 12.7 ± 11.7 | -2.0 ± 10.0 | 2.15 (0.43 ; 3.88) | 0.015 |
| Placebo | 166 | 13.2 ± 13.0 | 0.0 ± 10.4 | - | |

[†] Intention to Treat (ITT)+RDO Analysis
RDO: patients who stopped the treatment prematurely prior to evaluation under treatment; recalled and evaluated for this criterion at 24 weeks (n=19 rivastigmine, n=4 placebo)

[††] Covariance analysis with treatment and country as factors and initial ADAS-Cog as covariable – least squares method.

An improvement of at least 4 points in the ADAS-Cog (scored 0 to 70) was observed in 37% of the patients in the rivastigmine group and 29% of the patients in the placebo group.

In the subgroup of the patients with mild dementia (n=131), the variations in the ADAS-Cog scores were -2.6 (± 9.4) in the rivastigmine group (n=87) and 1.8 (± 7.2) in the placebo group (n=44). The adjusted difference *versus* placebo was 4.73 points.

In the subgroup of the patients with visual hallucinations (n=167), the variations in the ADAS-Cog scores were -1.0 (± 9.2) in the rivastigmine group (n=107) and 2.1 (± 8.3) in the placebo group (n=60). The adjusted difference *versus* placebo was 4.27 points.

Categorial analysis of the ADCS-CGIC data (score 1 to 7) revealed an odds ratio for the improved patients (score 1 to 3: marked, slight or minimal improvement) of 1.61 (IC 95% 1.07-2.44). Improvement was slight or marked (score 1 or 2) in 20% of the patients in the rivastigmine group and 14%

The post-hoc sensitivity analyses assigning the average scores in the placebo group obtained in the ITT+RDO population to non-evaluated patients (80 Exelon, 28 placebo) confirmed the difference *versus* placebo observed for the ADAS-Cog evaluation criteria (2.5 points) and ADCS-CGIC criteria in the ITT+RDO population. These analyses may, however, further overestimate the treatment effect by assigning the average score of the placebo group to patients who stopped the treatment because of intolerance.

Tolerance Data

131 patients stopped the treatment prematurely, before the end of the double-blind period:
- 27% (99/362) of the patients under rivastigmine (adverse event 17%, withdrawal of consent 6%)
- 18% (32/179) of the patients under placebo (adverse event 8%).

Of the adverse events causing discontinuation of the treatment, the most frequent were undesirable gastrointestinal effects (7.2% of the patients under rivastigmine *vs* 2.8% under placebo). Discontinuation of the treatment due to nausea was observed in 3.6% of the patients under rivastigmine and 0.6% of the patients under placebo. Disorders of the nervous system affected 5.2% of the patients under rivastigmine *versus* 2.2% under placebo (1.7% of the patients under stopped the treatment because of tremor).

A serious adverse event was reported in 47 patients under rivastigmine (13%) and 26 patients (14.5%) under placebo. Eleven deaths were reported (rivastigmine 4, placebo 7).

The most frequently reported adverse event under rivastigmine was cholinergic gastrointestinal effects (50.6% under rivastigmine vs 26.8% under placebo): nausea (29.0% vs 11.2%), vomiting (16.6% vs 1.7%). Hallucinations were reported in 9.5% of patients under placebo vs 4.7% under rivastigmine.

Adverse events occurring in at least 5 % of the patients in Exelon group

| Adverse events | Exelon (n=362) | Placebo (n=127) |
|---|---|---|
| Nausea | 29.0% | 11.1% |
| Vomiting | 16.6% | 1.7% |
| Tremor | 10.2% | 3.9% |
| Diarrhoea | 7.2% | 4.5% |
| Anorexia | 6.1% | 2.8% |
| Vertigo | 5.8% | 1.1% |
| Aggravation of the disease or Parkinsonian syndrome | 5.5% | 1.7% |

Pre-defined adverse events that may reflect worsening of parkinsonian symptoms were more frequent under rivastigmine (27.3%) than under placebo (15.6%). Tremors were reported in 10.2% of the patients under rivastigmine *vs* 3.9% under placebo. Aggravation of the disease was reported in 3.3% of the patients under rivastigmine *vs* 1.1% under placebo.

Of the adverse events possibly associated with the treatment (62.7% of the patients under rivastigmine, 39.7% under placebo), undesirable gastrointestinal effects were the most frequent (41.2% *vs* 15.1%): nausea (27.1% *vs* 8.4%), vomiting (14.6% *vs* 1.7%).

As regards the nervous system (23.8% *vs* 15.6%), tremors were observed in 8.6% of the patients under rivastigmine *vs* 3.4% of the patients under placebo.

<u>24-week open extension phase of treatment</u>
After 24 weeks of treatment, 334/433 eligible patients continued with the study and commenced the second period of treatment: rivastigmine 3 to 12 mg/d.

The initial dosage was 1.5 mg twice daily; this was increased in increments of 3 mg daily at intervals of at least 4 weeks during a 16-week titration period.

During the extension phase, 61/334 patients (18%) stopped the treatment prematurely: Adverse events (30 patients), withdrawal of consent (17 patients). Seven patients died.

The data on 273 patients were analysed. The average variations in the ADAS-Cog scores compared with the initial values at 48 weeks were -2 points in the group that had received rivastigmine for 48 weeks (n=162); The ADAS-Cog scores increased between weeks 24 and 48, denoting declining cognition. The average variation was -2.2 points in the patients who had received rivastigmine for 24 weeks, randomised patients in the placebo group during the double-blind phase (n=94).

The average ADCS-ADL variations at 48 weeks showed no improvement in the score compared with the initial values: 0.4 points in the group that had received rivastigmine for 48 weeks (n=162) and -0,8 points in the group that only started the active treatment from week 24.

Seventy five percent of the patients reported at least one adverse event: nausea (19% of the patients), vomiting (11%), and tremor (7%). These adverse events were observed more frequently in patients newly treated with rivastigmine, having received placebo until week 24. Aggravation of the Parkinsonian symptoms was observed in 18% of the patients.

Conclusion

The ENA713B2311 study compared the efficacy of rivastigmine (3 to 12 mg/d) with that of the placebo over a 24-week period in patients with dementia associated with Parkinson's disease.

Analysis of the adjusted average variations in the ADAS-Cog scores (scored 0 to 70) observed under rivastigmine (3 and 12 mg/d) showed a modest improvement in cognitive functions *versus* placebo (2.9 points).

In the subgroup of the patients with mild dementia (n=131), the adjusted difference *versus* placebo was 4.73 points. In the subgroup of the patients with visual hallucinations (n=167), the adjusted difference *versus* placebo was 4.27 points.

Validated in the cortical dementia of Alzheimer's disease, the ADAS-Cog scale is used here to evaluate a medicinal product used to treat the subcortical dementia of Parkinson's disease. The diagnosis of dementia in Parkinson's disease is based on the association of a severe dysexecutive syndrome and impaired mental and mnesic efficiency, in the absence of the aphasic, apraxic or agnosic signs that characterise Alzheimer's disease; employing the motor function required in order to reply to certain items in the ADAS-Cog scale may render it less suitable for Parkinsonian patients with major movement disorders.

Categorial analysis of the percentages of improved patients on the ADCS-CGIC scale (scored 1 to 7) revealed an odds ratio of 1.6 (IC 95% 1.07; 2.44) *versus* placebo; a moderate or marked improvement was observed in only 20% of the patients under rivastigmine *versus* 14% of the patients under placebo.

Analysis of the adjusted average variations in the ADCS-ADL scores (scored 0 to 78) showed a modest improvement in these scores under rivastigmine *versus* placebo (2.5 points).

The study evaluated the short-term benefit of a treatment using rivastigmine, but not the benefit of the treatment beyond 24 weeks.

### 3.1.2 Exploratory Study

The severity of the dysexecutive syndrome determines the severity of the dementia in Parkinson's disease. This syndrome can be evaluated using a global scale such as the Mattis scale[9], which includes five sections exploring attention, initiation, visuo-constructive praxis, reasoning abilities and memory. This global cognitive efficiency scale, used in subcortico-frontal dementias, would be more appropriate to the diagnosis and monitoring of dementia in Parksinson's disease. The maximum score is 144; a score of less than 30 is regarded as abnormal (although interpretation must take the patient's cultural level into account).

With the ENA713B2311 study, variations in the score on the Mattis scale were evaluated in 28 randomised patients (16 patients under rivastigmine, 12 patients under placebo).

For these patients, the average age of the disease was 14 to 16 years, that of the diagnosis of dementia approximately two years. The initial scores on the Mattis scale were 111 in the rivastigmine group and 105 in the placebo group.

At 24 weeks, the average variations compared with the initial values differed between the two groups: 5.79 (± 12.99) for the group under rivastigmine *versus* -0.42 (± 13.54) under placebo.

## 3.2. Adverse events

These data are from the pivotal study and its open extension phase conducted during clinical development in the indication.

9 Mattis Scale: 5 Subscales: attention, verbal and motor initiation, visuospatial construction, conceptualisation, verbal and non-verbal memory. 37 items (scored from 0 to 144). A high score indicates a less serious condition. Mattis S (1976), Smith GE (1994).

Three hundred sixty two patients were exposed to rivastigmine (3 to 12 mg/d) during the double-blind *versus* placebo pivotal study, and 334 patients during the 24-week extension phase.

In the pivotal study, in the patients under rivastigmine, the most frequently observed adverse events were cholinergic: nausea (29% *vs* 11% under placebo), vomiting (17% *vs* 2%) and tremor (10% *vs* 4%).

One hundred and thirty one patients stopped the treatment prematurely, before the end of the double-blind period: 27% of the patients under rivastigmine stopped the treatment prematurely *vs* 18% of the patients under placebo. Adverse events were the most common reason for discontinuing the study (17% of the patients under rivastigmine): nausea, 3.6 % of the patients, tremor 1.7%.

In the extension phase of the study, nausea was reported in 19% of the patients, vomiting in 11% and tremor in 7%. Aggravation of the Parkinsonian symptoms was observed in 18% of the patients.

### 3.3. Conclusion

Among the patients with slight to moderate the short-term associated with Parkinson's disease, the ENA713B2311 study showed a modest and a short term improvement in cognitive functions measured on the ADAS-Cog scale (2.9 points compared with the placebo on a 70-point scale). An improvement of at least 4 points on the ADAS-Cog scale was observed in 37% of the patients in the rivastigmine group and 29% of the patients in the placebo group.

Variations in the ADCS-CGIC scores, the overall change evaluated by the investigator, revealed a moderate or marked improvement in only 20% of the patients under rivastigmine *versus* 14% under placebo. A modest improvement was observed in the scores used to evaluate activity in daily life (2.5 points compared with the placebo on a 78-point scale).

Analysis of the adverse events observed in the patients under rivastigmine showed them to be cholinergic. Undesirable gastrointestinal reactions were the most frequent: nausea (29% *vs* 11%), vomiting (17% *vs* 2%).

Like other cholinomimetics, rivastigmine can exacerbate or induce extrapyramidal symptoms. Ten percent of the patients treated with rivastigmine presented motor aggravation of the tremor type *versus* 4% under placebo.

Prescribing rivastigmine for elderly patients, often polymedicated, mainly by cardiotropic and psychotropic agents, must take account of the risks inherent in drug interactions.

The Committee has noted the absence of comparative efficacy data for periods of treatment longer than six months.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual Benefit

Parkinson's disease is characterised by tremor at rest, rigidity, bradykinesia or akinesia and loss of postural reflexes. As the disease progresses, neurovegetative disorders, sensitive/painful complaints and mental disorders occur in addition to the motor disorders.

The onset of Parkinson's disease is usually insidious. It progresses slowly and is characterised by a progression towards a disability condition and a marked deterioration of the quality of life. It is life-threatening.

Subcortical dementia in Parkinson's disease increases the difficulties encountered by the healthcare auxiliaries as well as the dependency on daily care, reduces the patient's quality of life and increases mortality.

This proprietary drug is a symptomatic treatment.

With this drug, the short-term (24 weeks) efficacy/ adverse events ratio is modest. The long-term efficacy/ adverse events ratio remains to be determined.

There is no alternative treatment in this indication.

Public health benefit:

The public health burden of mild to moderately severe dementia associated with idiopathic Parkinson's disease is modest.

Improving the management of AMD is a public health requirement (a GTNDO [National Technical Group for Defining Public Health Objectives] priority).

Given the data available at 24 weeks, it is not possible to quantify the expected effect of Exelon on morbidity and the quality of life. The data are not sufficient to assess the effect of a longer-term treatment of this chronic condition. Maintaining treatment with Exelon is subject to regular reassessment by the doctor of the clinical benefit achieved. This raises the question of what criteria will govern this reassessment in practice.

Consequently, Exelon is not expected to have a public health benefit for this indication.

The actual benefit achieved with this proprietary medicinal product in this indication is moderate.

### 4.2. Improvement in Actual Benefit

Given the modest benefit observed and the risk of by no means negligible adverse reactions, Exelon provides a minor improvement in actual benefit (IAB IV) to patients with mild to moderately severe dementia associated with idiopathic Parkinson's disease. The Commission notes that patients with visual hallucinations may particularly benefit from rivastigmine.

### 4.3. Therapeutic use

Parkinsonian dementia is the manifestation of a severe subcortico-frontal syndrome.

The treatment of sever cognitive disorders requires the identification and elimination of iatrogenic factors:

- adjusting the dosage rates of dopaminergic drugs is a common procedure in the treatment of severe cognitive disorders in Parkinson's disease;
- the administration of drugs with anticholinergic properties (antispasmodics, bronchodilators, antitussives, imipraminic antidepressants, H1-antihistamines, antiarythmics, neuroleptics, anti-emetics, etc.…), which are very widely prescribed for elderly patients, may have undesired central effects, mainly on their mnesic and attentional abilities.

The recent and unusual occurrence of hallucinations must primarily involve examining the possibility that the cause lies in the drug. It may be decided to use a neuroleptic drug of the clozapine type before the onset of these disorders.

Severe cognitive disorders require treatments other than drugs, such as the active support of the patient and his or her entourage, and specific therapies designed to optimise reality orientation so as to improve the patient's cognitive functions and behaviour.

Rivastigmine is an anticholinesterase indicated for the treatment of mild to moderately severe dementia associated with idiopathic Parkinson's disease.

The clinical benefit of rivastigmine must be assessed three months after the introduction of a well-tolerated treatment. The treatment may only be maintained following clinical reassessment of the benefit/risk of the drug; this should be carried out at regular intervals.

### 4.4. Target Population

Global mental deterioration may arise in the course of Parkinson's disease and a demential picture, meeting the DSM (DSM-III-R or IV) criteria of dementia was effectively observed in 17.6% of the 60 Parkinson's disease patients in the Paquid cohort, a huge sample representing the over-65 population[i]. Brown and Marsden[ii] reported prevalences of 15 to 20%. More recently, in a review of the literature, Aarsland[iii] pointed to a slightly higher prevalence, of the order of 25 to 30%, whilst emphasising the considerable variations from one study to another.

The number of Parkinson's disease patients in France is estimated at between 110,000 and 145,000. Extrapolating these figures to the French population would be the Exelon target population between 14,000 and 30,000 patients.

### 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 indication extension "Symptomatic Treatment of Mild to Moderately Severe Dementia in Patients with Idiopathic Parkinson's Disease" and for the dosage indicated in the Marketing Authorisation.

4.5.1 Packaging : Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 35%

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[i] Tison F. et al. Dementia in Parkinson's disease: a population-based study in ambulatory and institutionalized individuals. Neurology 1995;45:705-8.

[ii] Brown and Marsden. How common is dementia in Parkinson's disease? Lancet 1984;2:1262-5.

[iii] Aarsland D. et col. A systematic review of prevalence studies in dementia in Parkinson's disease. Movement disorders 2005;20:1255-63.