HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
18 December 2013

EXELON 13.3 mg/24 hours, transdermal patch
B/30 sachets (CIP: 34009 268 908 1 0)

Applicant: NOVARTIS PHARMA S.A.S.

INN	rivastigmine
ATC code (2012)	N06DA03 (anti-dementia drugs, anticholinesterases)
Reason for the request	**Inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Symptomatic treatment of mild to moderately severe Alzheimer's dementia. "**

Actual Benefit	**Insufficient to justify reimbursement by the social security system in the "symptomatic treatment of mild to moderately severe Alzheimer's dementia."**
Improvement in Actual Benefit	**Not applicable**
Therapeutic Use	**Not applicable**
Target population	**Not applicable**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (European centralised procedure)	Date initiated: 14 January 2013
Prescribing and dispensing conditions / special status	List I Medicine requiring special monitoring during treatment. Initial annual prescription reserved for specialist prescribers in neurology and in psychiatry, and specialists prescribers holding a diplôme d'études spécialisées complémentaires [diploma of further specialised studies] in geriatrics and specialists prescribers or general prescribers holding a qualification in gerontology.

ATC Classification	2012	
	N	Nervous system
	N06	Psychoanaleptics
	N06D	Anti-dementia drugs
	N06DA	Anticholinesterases
	N06DA03	Rivastigmine

02 BACKGROUND

This is a review of the application for inclusion of the EXELON transdermal patch 13.3 mg/24 hours on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use. This new dose complements other doses of EXELON transdermal patch (4.6 mg/24 hours and 9.5 mg/24 hours), and oral forms (EXELON 1.5 mg, 3 mg, 4.5 mg and 6 mg, capsule, EXELON 2 mg/ml, oral solution).

03 THERAPEUTIC INDICATIONS

"Symptomatic treatment of mild to moderately severe Alzheimer's dementia."

04 DOSAGE

"Initial dose: the treatment should be initiated with the dose of 4.6 mg/24 hours.

Maintenance dose: after a minimum of four weeks of treatment and if well tolerated according to the treating physician, the dose of 4.6 mg/24 hours may be increased to 9.5 mg/24 hours, the daily recommended effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit.

Dose escalation: 9.5 mg/24 hours is the recommended daily effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If the treatment of 9.5 mg/24 hours is well tolerated, and only after a minimum of six months of treatment, the treating physician may consider increasing the dose to 13.3 mg/24 hours to obtain an additional therapeutic benefit in patients who have demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the daily recommended effective dose of 9.5 mg/24 hours. The clinical benefit of rivastigmine should be re-assessed on a regular basis. Discontinuation should also be considered when evidence of a therapeutic effect at the optimal dose is no longer present."

05 THERAPEUTIC NEED

Alzheimer's dementia is a severe, disabling, degenerative neurological disease of the central nervous system, with considerable repercussions on family and social life. The symptoms of dementia are characterised by a progressive deterioration in cognitive function: memory, language and attention, visuospatial function, the executive functions of anticipating, initiating and planning tasks, self-awareness and awareness of one's environment, ability to perform purposeful movements (praxis) and to recognise living beings and objects (gnosis). These disorders are accompanied by a significant impact on the patient's working and social life. The disease mostly develops progressively, with a worsening of cognitive disorders and dependence (loss of patient autonomy) in relation to all activities of daily living, and impairment of behaviour, which become increasingly difficult for family members to tolerate (apathy, agitation, aggressiveness, wandering, delirium and hallucinations). Other forms of dementia generally do not develop in such a prolonged, insidious and chronic manner. Patient autonomy is gradually reduced over the course of the illness. When loss of autonomy is complete, the patient has to be admitted to a specialist institution.

Specific drug treatment is an option, the initiation or renewal of which is left to the prescribing doctor's discretion. This discretion should take into account the patient's preferences and the risk-benefit ratio of the drug treatment planned. The treatments are initiated at the minimum dose, with the dosage possibly being gradually increased until the maximum dose recommended and tolerated. Seeing the patient again 1 month later is recommended so as to assess drug safety and so that the dosage can be adjusted either by the primary prescribing doctor or the generalist physician or any other specialist who is monitoring the patient. In the event of intolerance or failure to reach the maximum doses recommended, it is possible for a treatment to be substituted for another. A specific drug treatment should only be continued for more than 6 months after careful re-assessment. If the objectives set for the treatment (for instance, stabilisation or slowing of cognitive decline) are achieved and if no serious adverse effects and/or effects on quality of life have occurred, this treatment may be continued for one further period. At the end of one year, it should be decided whether to continue the treatment after discussions with the carer and the patient if possible, following a team meeting involving the treating doctor, geriatrician and neurologist or psychiatrist, taking into account the care network under which the patient is being treated, and on condition that efficacy has been maintained for one year.[1]

[1] HAS (Haute Autorité de Santé). Alzheimer's disease and related diseases: diagnosis and management. Recommendations. December 2011.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

They are:

- three other anticholinesterase inhibitors also indicated in the "symptomatic treatment of mild to moderately severe Alzheimer's dementia" administered orally.
- memantine (EBIXA). It should be noted that it does not have marketing authorisation in mild forms of Alzheimer's dementia, and that it is the only one of these medicinal products to be also indicated in severe forms of the disease.

These medicinal products are presented in Table 1.

06.2 Other health technologies

Non-drug interventions, an important part of patient care whose main purpose is to fight against cognitive decline linked to dementia, were subject to recommendations in 2011, in France by HAS,[2] and in Belgium by the KCE.[3] The non-drug interventions recommended are in particular those relating to the patient's quality of life, the psychological and psychiatric care of the patient and his/her family, language therapy, cognition, motor activity or the behaviour of the patient.

◗ Conclusion:

The relevant comparators of EXELON 13.3 mg/24 hours in the symptomatic treatment of Alzheimer's dementia are:

- **in mild to moderately severe Alzheimer's disease: three other anticholinesterase inhibitors: donepezil (ARICEPT), galantamine (REMINYL) and rivastigmine (EXELON p.o.).**
- **in moderate to severe forms: memantine (EBIXA).**

[2] HAS (Haute Autorité de Santé). Alzheimer's disease and related diseases: diagnosis and management. Recommendations. December 2011.

[3] KCE (Belgian Health Care Knowledge Centre). Dementia: which non-pharmacological interventions? KCE reports 160B. July 2011.

Table 1: pharmaceutical proprietary medicinal products with a marketing authorisation in the indication "Symptomatic treatment of mild to moderately severe Alzheimer's disease".

PROPRIETARY MEDICINAL PRODUCT Company	INN	Pharmacotherapeutic class	Indication	Date of opinion	AB	IAB	Reimbursement
EXELON capsule oral solution *NOVARTIS*	rivastigmine	IAChE	Symptomatic treatment of mild to moderately severe Alzheimer's dementia	19/10/2011	Low	Level V (absence of improvement) in the symptomatic treatment of mild to moderately severe Alzheimer's dementia	Yes
ARICEPT orodispersible tablet film-coated tablet *EISAI*	donepezil						
REMINYL film-coated tablet extended-release capsule oral solution *JANSSEN CILAG*	galantamine						
EBIXA film-coated tablet oral solution *LUNDBECK*	memantine	Another class (NMDA)	Symptomatic treatment of moderate to severe Alzheimer's dementia			Level V (absence of improvement) in the symptomatic treatment of moderate to severe Alzheimer's dementia	

NMDA: N-Methyl-D-aspartate receptor antagonists
IAChE: acetylcholinesterase inhibitor

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation overseas

EXELON 13.3 mg/24 hours has a marketing authorisation in the USA since August 2012. The dosage category in the North American SmPC [4] specifies that: "The effective dose for EXELON transdermal patch is 9.5 mg/24 hours or 13.3 mg/24 hours administered once a day, to be replaced by a new transdermal patch every 24 hours. … Start the treatment with EXELON 4.6 mg/24 hours, transdermal patch, to be applied to the skin once a day.
Dose titration: Increase the dose only after a minimum of 4 weeks following the previous dose, and only if the previous dose was well tolerated. Continue the recommended effective dose of 9.5 mg/24 hours for as long as the therapeutic benefit continues. The dose can then be increased to the maximum effective dose of 13.3 mg/24 hours. Doses higher than 13.3 mg/24 hours do not provide any additional considerable benefit, and are linked to an increase in the occurrence of adverse effects." According to the North American SmPC, this may lead to an increase in the dose of the rivastigmine transdermal patch (13.3 mg/24 hours) as soon as the patient is no longer receiving any benefit from the recommended daily effective dose (9.5 mg/24 hours), and not only after a minimum of 6 months' treatment, as is specified in the European SmPC.

08 SUMMARY OF PREVIOUS ASSESSMENTS

The previous assessments of EXELON in the "symptomatic treatment of mild to moderately severe Alzheimer's disease" are summarised in Table 2.

Table 2: Previous assessments of the EXELON range in the "symptomatic treatment of mild to moderately severe Alzheimer's disease."

Type of assessment	EXELON 1.5 mg, 3 mg, 4.5 mg and 6 mg capsule	EXELON 2 mg/ml oral solution	EXELON 4.6 mg/24 hours and 9.5 mg/24 hours transdermal patch
Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use	03/06/1998 Substantial AB - IAB II	19/05/2004 Substantial AB - IAB II	05/12/2007 Substantial AB - IAB V
Renewal of inclusion	18/04/2001 Substantial AB	-	-
Renewal of inclusion	20/06/2007 Substantial AB - IAB IV	20/06/2007 Substantial AB - IAB IV	-
Re-assessment and renewal of inclusion	19/10/2011 Low AB - IAB V	19/10/2011 Low AB - IAB V	19/10/2011 Low AB - IAB V

Reminder of the conclusions of the opinion on the re-assessment of 19 October 2011 (see assessment report on medicines indicated in the symptomatic treatment of Alzheimer's dementia):

[4] FDA (Food and Drug Administration). Exelon Patch (rivastigmine transdermal patch). Full Prescribing Information. August 2012.

AB:

" - Although it is impossible to identify responding patients a priori, in order not to deprive certain patients of the possible slight clinical benefit observed in the short term with medicinal products for the symptomatic treatment of Alzheimer's dementia, the actual benefit of EXELON should be considered to be low.

- In the absence of long-term clinical data, treatment with EXELON should only be continued beyond six months after careful re-assessment. If the patient has achieved the objectives set for his/her treatment (for instance, stabilisation or slowing of cognitive decline) and if no serious adverse effects or effects on quality of life have occurred, treatment with EXELON may be continued for one further period.

- The Committee proposes that continuing treatment beyond one year should be decided after discussions with the carer and the patient if possible, following a multidisciplinary meeting involving the treating doctor, geriatrician and neurologist or psychiatrist, taking into account the care network under which the patient is being treated, and on condition that efficacy has been maintained for one year."

IAB:

"The Transparency Committee considers that EXELON does not provide any improvement in actual benefit (IAB V) in the symptomatic treatment of mild to moderately severe Alzheimer's dementia. This opinion is based on the available clinical data on efficacy, which reveal an effect size that is at best modest, established over the short term and mainly on cognitive disorders, the risk of onset of adverse effects and drug interactions and on the lack of data demonstrating long-term therapeutic benefit."

09 ANALYSIS OF AVAILABLE DATA

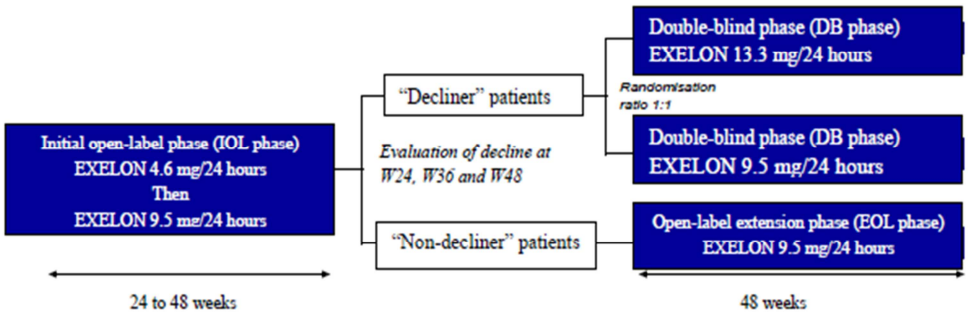
The company presented the results of a clinical study (OPTIMA) comparing the efficacy of two doses of rivastigmine administered as a transdermal patch and safety data in patients with Alzheimer's disease.
No study has compared the EXELON transdermal patch 13.3 mg/24 hours with another anticholinesterase inhibitor or memantine.

09.1 Efficacy

The aim of this OPTIMA study (OPtimising Transdermal Exelon In Mild-to-Moderate Alzheimer's disease) [5] was to compare the efficacy and the adverse effects of EXELON 13.3 mg/24 hours (increase in the dosage) versus EXELON 9.5 mg/24 hours (continuation of the same dosage) in patients at a mild to moderately severe stage of Alzheimer's disease and with signs of cognitive and functional decline after receiving treatment with the EXELON transdermal patch 9.5 mg/24 hours for 24 to 48 weeks.

Study design
This is a controlled, randomised, double-blind, parallel-group study which took place from June 2007 to May 2011. The study, which lasted a total of 72 to 96 weeks, comprised two periods:
- open-label period of 24 to 48 weeks (IOL phase) where the patients received EXELON 9.5 mg/24 hours;
- second period of 48 weeks, randomised and comparative (DB phase), where the patients in the open-label period in weeks 24, 36 and 48 and defined as "decliners" were randomised in two groups: EXELON 9.5 mg/24 hours (once a day) or EXELON 13.3 mg/24 hours (once a day), according to a ratio of 1/1. The patients defined as "non-decliners" were able to continue the study by continuing the treatment with EXELON 9.5 mg/24 hours.

The eligibility criteria of the patients at the start of the comparative phase were the presence of cognitive and functional decline and the absence of intolerance to the EXELON patch 9.5 mg/24 hours in the course of the open-label (IOL) phase. The cognitive decline was evaluated by the investigators. The functional decline was evaluated by a decrease of ≥ 2 points in the MMSE score compared with the previous visit, or a decrease of ≥ 3 points in the MMSE score compared with the baseline value of the IOL phase. The decline was evaluated in weeks 24, 36 and 48 of the IOL phase. Adjustments in dose and interruptions in treatment were permitted for patients who were unable to tolerate the specified dose until their tolerance improved.
The patients who did not respond to the criteria of decline ("non-decliner patients") had the option of starting an open-label extension phase (EOL phase) by continuing the treatment with EXELON 9.5 mg/24 hours. The study design and the interventions are summarised in Figure 1:



[5] Cummings J, Froelich L, Black SE, *et al*. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm²) in Alzheimer's disease. Dement Geriatr Cogn Disord. 2012;33(5):341-53.

Treatments evaluated during the comparative phase
EXELON 9.5 mg/24 hours or 13.3 mg/24 hours.

Inclusion criteria:
- adult aged 50 to 85 years old with a diagnosis of Alzheimer's dementia made in the two years preceding inclusion in the study, according to DSM-IV[6] or NINCDS/ADRDA[7] criteria, with an MMSE[8] score between 10 and 24;
- patient not living alone or having daily contact with a responsible carer.
- treatment with memantine (EBIXA) for at least 3 months was possible.

Non-inclusion criteria included:
- vascular dementia
- patients with a history of cerebrovascular disease (stroke, TIA, aneurysm)
- uncontrolled epilepsy; severe and/or unstable cardiovascular disease, bradycardia (≤ 50 beats per minute), sick sinus syndrome or cardiac conduction abnormalities; uncontrolled gastric ulceration and gastrointestinal bleeding (in the previous 3 months); clinically significant obstruction of the urinary tract; skin lesions preventing the use of a transdermal patch.
- no intolerance to the EXELON transdermal patch 9.5 mg/24 hours
- intake of anticholinesterase inhibitors or other treatments indicated in Alzheimer's disease in the 2 weeks preceding the inclusion.

Endpoints
Two co-primary efficacy endpoints were analysed at the end of the 48 weeks of the comparative phase:
- change in the ADCS-IADL score of the instrumental subscale of the ADCS-ADL[9] scale, which aims to evaluate the development of functional autonomy;
- change in the score of the cognitive subscale of the ADAS-cog[10] scale.

Secondary efficacy endpoints
- the time before functional decline during the DB phase measured by the time interval between the baseline value and the first decline on the ADCS-IADL scale, evaluated by a decrease of ≥ 1 point in the ADCS-IADL score during one visit and confirmed during the following visit, or a decrease of ≥ 2 points in the ADCS-IADL score compared with the baseline value of the DB phase;
- the change in the TMT-A and TMT-B (Trail Making Test parts A and B) scores between the baseline value and week 48 of the DB phase, which aims to evaluate the development of attention and executive functions;
- the change in the NPI-10 (NeuroPsychiatric Inventory - 10 items) score between the baseline value and week 48 of the DB phase, which aims to evaluate the development of neuropsychiatric symptoms;
- the change in the NPI-D (NeuroPsychiatric Inventory - Caregiver Distress Scale) score between the baseline value and week 48 of the DB phase, which aims to evaluate the distress of the caregiver.

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[6] DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition.
[7] NINCDS/ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.
[8] MMSE: *Mini-Mental State Examination*
[9] The ADCS-IADL score corresponds to the instrumental activities of daily living (items 7 to 23) of the ADCS-ADL scale (Alzheimer's Disease Cooperative Study - Activities of Daily Living). This scale evaluates the "basic" activities (washing, mobility, dressing) and the instrumental activities (shopping, budgeting, transport etc.) of daily life. The company indicates that the analysis of the results for the registration trial for the patch 9.5 mg/24 hours having shown insensitivity to change over 6 months, in the placebo groups and treated groups, in terms of the basic activities (items 1 to 6), it was decided, after consulting experts, to only measure the instrumental activities (items 7 to 23) in the OPTIMA study.
[10] ADAS-Cog: Alzheimer's Disease Assessment Scale - Cognitive Subscale.

Statistical analyses

The populations evaluated were defined as follows:
- ITT population: randomised patients who received at least one dose of study drug during the DB phase and for whom at least one post-randomisation evaluation of the two co-primary efficacy endpoints was available.
- Per-protocol population (PP): patients from the ITT population who have not had any major deviation in the study protocol during the DB phase and for whom at least one post-randomisation evaluation of the two co-primary efficacy endpoints was available as of week 24 of the DB phase.

The methods of analysis of the two co-primary efficacy endpoints were determined as follows:

The changes in each of the ADCS-IADL and ADAS-cog scores between the baseline value of the DB phase and week 48 of the DB phase in the two treatment groups were compared by analysing the difference in the mean values obtained by the method of least squares [LS], applied after the analysis of covariance, integrating the treatment, the country and the score with the baseline value of the DB phase as explicative factors.

In order to test the robustness of the analyses of the two co-primary efficacy endpoints, sensitivity analyses were performed on the ITT population (the de van Elteren non-parametric test, mixed-effect repeated-measures model, multiple imputation for data missing at random, scenarios of data missing not at random with penalty scores). The analyses were performed on the ITT population using the method of imputation of the last observation carried forward [ITT-LOCF]. Analyses were also conducted on the ITT population using the non-imputation method for the observed cases [ITT-OC], as well as on the PP population using the LOCF [PP-LOCF] method and the OC method [PP-OC].

Calculation of sample size:

In order to detect a difference of 1.9 points between the study drugs for each of the two co-primary efficacy endpoints among the patients in the ITT population at the end of the DB phase (2-tailed student's t-test, with a degree of significance of 0.05, a power of 0.85, an implied standard deviation of 8 points for the two co-primary efficacy endpoints, an implied correlation of 0.35 between the two co-primary efficacy endpoints), the sample size was estimated to be 820 patients, that is 410 patients per group.

Assuming 5% of patients could not be included in the ITT population, a total of 864 patients, that is 432 patients per group, was estimated to be necessary for the randomisation. Assuming 55% of patients had a cognitive decline during the IOL phase and so as to ensure that at least 864 patients had a decline allowing them to take part in the randomisation, it was thus estimated that 1,571 patients had to be included in the IOL phase.

Analysis of the secondary endpoints

The analysis of the time before functional decline during the DB phase, measured by the time interval between the baseline value of the DB phase and the first decline on the ADCS-IADL scale, was subject to an analysis of the ITT population using a log-rank test on the interval censored data from the [ITT-OC] method.

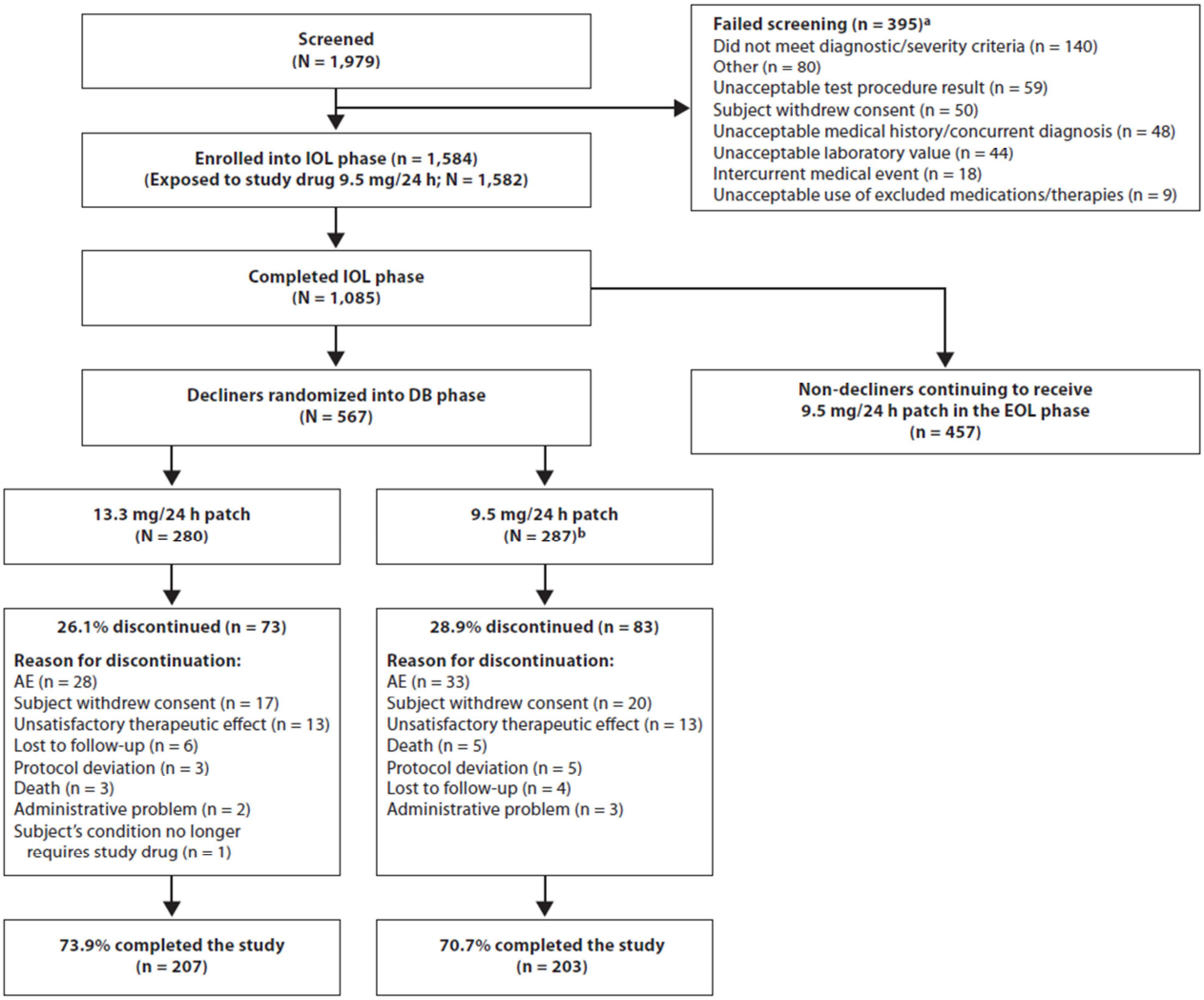
The changes in each of the TMT-A, TMT-B, NPI-10 and NPI-D scores between the baseline value of the DB phase and week 48 of the DB phase in the two treatment groups were compared for the ITT population using the method of least squares [LS], applied after the analysis of covariance, integrating the treatment, the country and the score with the *baseline* value of the DB phase as explicative factors, the data of which was from the [ITT-LOCF] and [ITT-OC] methods.

Results:

The patients were recruited in 147 centres located in seven countries, including five European (Italy, Germany, France, Switzerland and Spain) and two North American (United States and Canada). The number of patients included in France was 129 (<10% of the total number).

The number of subjects analysed and the times the treatment was discontinued are summarised in Figure 2.

Figure 2: Summary of the number of subjects analysed and the times the treatment was discontinued in the OPTIMA study.



Number of subjects analysed

Among the 1,979 patients who underwent an evaluation for participating in the study, 1,582 patients (79.9%) started a treatment with EXELON 9.5 mg/24 hours during the open-label period and 1,085 patients (68.6%) ended this period.

Among the 1,085 patients who ended the open-label period, 567 "decliner" patients (52.3%) were included in the DB phase, 457 "non-decliner" patients (42.1%) were included in the EOL phase and 61 "non-decliner" patients (5.6%) or patients who did not tolerate the standard maintenance dose of rivastigmine (EXELON 9.5 mg/24 hours) ended the study at this stage. Among the 567 "decliner" patients included for the DB phase, 280 patients were randomised in the EXELON 13.3 mg/24 hours group and 287 in the EXELON 9.5 mg/24 hours group. Among the 567 randomised patients, 410 patients (72.3%) ended the comparative phase, 207 patients (73.9%) in the EXELON 13.3 mg/24 hours group and 203 patients (70.7%) in the EXELON 9.5 mg/24 hours group.

Number and reasons for the patients discontinuing the treatment

Among the 1,582 patients who received EXELON 9.5 mg/24 hours during the open-label phase, 497 patients (31.4%) discontinued the treatment. The causes for patients discontinuing the treatment during this period of the study were not indicated.

Among the 567 randomised patients, 156 patients (27.5%) discontinued the treatment during the DB phase, 73 (26.1% in the EXELON 13.3 mg/24 hours group and 83 (28.9%) in the EXELON 9.5 mg/24 hours group. The main causes for patients discontinuing the treatment were the occurrence of adverse effects (28 in the EXELON 13.3 mg/24 hours group versus 33 in the EXELON 9.5 mg/24 hours group), the withdrawal of the patient's consent (17 in the EXELON 13.3 mg/24 hours group versus 20 in the EXELON 9.5 mg/24 hours group) and an insufficient therapeutic effect (13 in the EXELON 13.3 mg/24 hours group versus 13 in the EXELON 9.5 mg/24 hours group).

Characteristics of patients on inclusion in the comparative phase

They are largely similar (see Table 3).

Table 3: Characteristics of patients on inclusion in the DB phase of the OPTIMA study

Characteristic	EXELON 13.3 mg/24 hours N = 280	EXELON 9.5 mg/24 hours N = 287	Total population N = 567
Women, n (%)	185 (66.1)	182 (63.4)	367 (64.7)
Mean age (years)	75.6	75.9	75.7
Mean time since the appearance of the first symptoms of Alzheimer's disease notified by the patients or their carers (years)	3.9	4.3	4.1
Mean time since the Alzheimer's disease was diagnosed (years)	1.8	2.0	1.9
Mean MMSE score	14.1	14.2	14.2
ADCS-IADL score	27.5	25.8	26.65
ADAS-cog score	34.4	34.9	34.65
Concomitant treatment by memantine, n (%)	92 (32.9)	90 (31.8)	182 (32.3)

Concomitant treatments during the DB phase

The percentage of patients receiving at least one antipsychotic, antidepressant or hypnotic/anxiolytic drug was 30.0% in the EXELON 13.3 mg/24 hours group and 31.1% in the EXELON 9.5 mg/24 hours group. Almost 20% of patients started study drugs during the DB phase with at least one drug from these three classes.

The percentage of patients receiving an antidepressant drug was 10.0% in the EXELON 13.3 mg/24 hours group and 8.5% in the EXELON 9.5 mg/24 hours group for a duration of treatment of 37.0 weeks in the EXELON 13.3 mg/24 hours group versus 39.8 weeks in the EXELON 9.5 mg/24 hours group.

The percentage of patients receiving an antipsychotic drug was 8.9% in the EXELON 13.3 mg/24 hours group and 9.9% in the EXELON 9.5 mg/24 hours group for a duration of treatment of 26.7 weeks in the EXELON 13.3 mg/24 hours group versus 29.5 weeks in the EXELON 9.5 mg/24 hours group.

The percentage of patients receiving a hypnotic/anxiolytic drug was 6.1% in the EXELON 13.3 mg/24 hours group and 6.4% in the EXELON 9.5 mg/24 hours group for a treatment duration of 33.0 weeks in the EXELON 13.3 mg/24 hours group and 33.2 weeks in the EXELON 9.5 mg/24 hours group.

Efficacy results (ITT population)
The ITT population was 536 patients (94.5% of randomised patients), 265 in the EXELON 13.3 mg/24 hours group and 271 in the EXELON 9.5 mg/24 hours group.

Primary efficacy endpoints:
- ADCS-IADL score (co-primary efficacy endpoint): functional decline was observed in the two groups. After 48 weeks of treatment, the change in the ADCS-IADL score was - 4.4 points in the EXELON 13.3 mg/24 hours group and - 6.2 points in the EXELON 9.5 mg/24 hours group, that is, according to the [ITT-LOCF] analysis, a difference of 2.2 points in favour of the high dose (95% CI = [0.8; 3.6], *p* = 0.002).
- ADAS-cog score (co-primary efficacy endpoint): cognitive decline was observed in the two groups, and after 48 weeks of treatment, no difference was observed between the two groups. The change in the ADAS-cog score was + 4.1 points in the EXELON 13.3 mg/24 hours group versus + 4.9 points in the EXELON 9.5 mg/24 hours group, that is, according to the [ITT-LOCF] analysis, an NS difference of - 0.8 points (95% CI = [-2.1; 0.5], *p* = 0.227).

Results for the secondary endpoints:
- time before functional decline: the log-rank test does not allow any difference between the two treatment groups to be identified. The quantified data and the degree of significance were not given.
- TMT-A, TMT-B, NPI-10 and NPI-D scores: no difference was identified between the two treatment groups according to the ITT-LOCF analysis.

Table 4: Secondary efficacy endpoints at the end of the 48 weeks of the comparative phase of the OPTIMA study, changes in the TMT-A, TMT-B, NPI-10 and NPI-D scores.

Secondary endpoint	EXELON 13.3 mg/24 hours	EXELON 9.5 mg/24 hours	Difference in averages ([LS] method) [95% CI]	*p* value
TMT-A	+16.3	+18.2	-3.8 [-14.3; 6.6]	0.473
TMT-B	+9.3	+5.9	0.8 [-10.1; 11.8]	0.881
NPI-10	+1.4	+0.9	-0.1 [-1.9; 1.7]	0.927
NPI-D	+0.6	0.0	0.2 [-0.7; 1.2]	0.647

At the request of the CHMP, an analysis in terms of "responder patients" was performed. In the absence of valid response criteria for a population of decliner patients, defining the response to treatment was suggested as follows: at week 48, loss of ADAS-cog and/or ADCS-IADL of no more than 0, 2, 4, 6 and 8 points in relation to the randomisation. A larger proportion of "responder patients" in the 13.3 mg/24 hours group was identified for all the responder categories with the exception of the loss category of at least 8 points on the ADAS-cog scale. To achieve a definition of responders combining the cognitive and functional criteria (loss of no more than 4 points on the two scales), a difference in favour of the EXELON 13.3 mg/24 hours group was noted at week 48.

Table 5: Percentage of responder patients at the end of the 48 weeks of the comparative phase in the OPTIMA study

	EXELON 13.3 mg/24 hours	EXELON 9.5 mg/24 hours	*p* value
Loss of no more than 4 points on the ADAS-cog and ADCS-ADL scale	35.8%	28%	0.037

09.2 Adverse effects

The data come from the OPTIMA study, the last Periodic Safety Update Report (PSUR) and an international pharmacovigilance database. Significant changes to the European Summary of Product Characteristics are also presented.

09.2.1 OPTIMA study data

The data are those of the so-called "safety" population. It was defined by the randomised patients who received at least one dose of study drug during the DB phase and for whom at least one post-randomisation evaluation of the safety of study drug treatment was available. It comprises 563 patients (99.3% of randomised patients), 280 in the EXELON 13.3 mg/24 hours group and 283 in the EXELON 9.5 mg/24 hours group.

Death

The percentage of patients who died during the comparative phase was 1.1% in the EXELON 13.3 mg/24 hours group and 1.8% in the EXELON 9.5 mg/24 hours group, none of them considered as being linked to the treatments.

Serious adverse events (SAEs)

No unexpected serious adverse event was observed.

The percentage of patients who had an SAE during the comparative phase was similar between the two groups: 15.7% in the EXELON 13.3 mg/24 hours group versus 15.5% in the EXELON 9.5 mg/24 hours group. The most common were infections (4.6% in the EXELON 13.3 mg/24 hours group *versus* 4.2% in the EXELON 9.5 mg/24 hours group) and nervous system disorders (5.0% of patients in the EXELON 13.3 mg/24 hours group versus 3.9% in the EXELON 9.5 mg/24 hours group).

Discontinuation of treatment due to an adverse event (AE and SAE)

The percentage of patients who discontinued the treatment due to an AE was lower in the EXELON 13.3 mg/24 hours group (9.6% including 4.3% serious) than in the EXELON 9.5 mg/24 hours group (12.7% including 6.4% serious). The most common were gastrointestinal disorders, general disorders and abnormalities at the site of administration, and psychiatric disorders.

Occurrence of adverse events (AEs)

The percentage of patients who had at least one AE was greater in the EXELON 13.3 mg/24 hours group (75.0%) than in the EXELON 9.5 mg/24 hours group (68.2%). Likewise, the occurrence of the AE leading to a dose adjustment was also greater in the EXELON 13.3 mg/24 hours group (13.9%) than in the EXELON 9.5 mg/24 hours group (5.3%).

The most common, by type of organ, were gastrointestinal disorders (29.3% in the EXELON 13.3 mg/24 hours group *versus* 19.1% in the EXELON 9.5 mg/24 hours group), psychiatric disorders (25.4% in the EXELON 13.3 mg/24 hours group *versus* 21.6% in the EXELON 9.5 mg/24 hours group) and nervous system disorders (21.4% in the EXELON 13.3 mg/24 hours group *versus* 18.4% in the EXELON 9.5 mg/24 hours group).

Gastrointestinal cholinergic disorders (nausea, vomiting, loss of weight, loss of appetite, upper abdominal pain) were more common in the EXELON 13.3 mg/24 hours group (39.3% of patients) than in the EXELON 9.5 mg/24 hours group (15.9% of patients).

It should be noted that the occurrence of patients with a new abnormality on the ECG was similar between the two groups, that is 17.5% in the EXELON 13.3 mg/24 hours group and 15.2% in the EXELON 9.5 mg/24 hours group.

The most common AEs (≥ 3%) are summarised in Table 5.

Table 5: The most common AEs (≥ 3%) in the OPTIMA study.

Adverse event	EXELON 13.3 mg/24 hours n = 280 (%)	EXELON 9.5 mg/24 hours n = 283 (%)
Total	**210 (75.0)**	**193 (68.2)**
Nausea	34 (12.1)	14 (4.9)
Vomiting	29 (10.4)	13 (4.6)
Collapse	21 (7.5)	17 (6.0)
Loss of weight	19 (6.8)	8 (2.8)
Erythema at the application site	18 (6.4)	16 (5.7)
Loss of appetite	18 (6.4)	7 (2.5)
Diarrhoea	18 (6.4)	13 (4.6)
Urinary tract infections	15 (5.4)	12 (4.2)
Agitation	14 (5.0)	15 (5.3)
Depression	14 (5.0)	13 (4.6)
Dizziness	12 (4.3)	2 (0.7)
Pruritus at the application site	11 (3.9)	11 (3.9)
Headaches	11 (3.9)	11 (3.9)
Insomnia	11 (3.9)	7 (2.5)
Upper abdominal pains	10 (3.6)	3 (1.1)
Anxiety	10 (3.6)	7 (2.5)
Mental confusion	9 (3.2)	7 (2.5)
Hypertension	9 (3.2)	8 (2.8)
Urinary incontinence	9 (3.2)	5 (1.8)
Psychomotor hyperactivity	7 (2.5)	9 (3.2)
Aggression	6 (2.1)	9 (3.2)

09.2.2 Periodic Safety Update Report (PSUR)

Since the previous opinion from the Committee (19 October 2011), the PSUR for the period of 1st February 2011 to 31st January 2012 is now available. The exposure of patients to different EXELON transdermal patches was estimated to be about 506,000 patient-years of treatment. No change (new signal, frequency, severity of AE already known) has been reported from spontaneous notifications received during this period.

09.2.3 Pharmacovigilance database

The data presented are from the international pharmacovigilance database held by the company. They cover the period of 10 August 2009 to 30 September 2012. They come from spontaneous notifications made in Brazil (first country in which EXELON 13.3 mg/24 hours was marketed) and include observations not confirmed medically. The exposure of patients to the treatment was estimated to be about 9,000 patient-years of treatment. During this period, there were 438 AEs, including 130 that were thought to be serious.

The most common adverse events were the following: local reactions at the application site (35), vomiting (27), nausea (26), memory impairment (21) and incorrect technique when using the transdermal patch (17).

09.2.4 Changes made to the European SmPC

Significant changes to the safety section of the European SmPC for EXELON transdermal patches have been made since the previous opinion from the Committee.
Change of 23 May 2011:

- addition of special warnings and precautions for use relating to adverse effects of the gastrointestinal disorder type;

- addition of the following adverse effects observed in patients suffering from Alzheimer's disease and treated with the EXELON range of transdermal patches during a clinical study (frequency not known): dehydration, aggressiveness, agitation, worsening of Parkinson's disease, convulsions, atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome, hypertension, pancreatitis, hepatitis, pruritus, erythema, urticaria, vesicles, allergic dermatitis, falls.

Change of 16 November 2011:
- addition of the following adverse effect: elevated liver enzymes (frequency not known), observed in patients suffering from Alzheimer's disease and treated with the EXELON range of transdermal patches during a clinical study.

Change of 20 April 2012:
- addition of a contraindication in the event of a history of allergic reaction suggesting allergic dermatitis on contact with the EXELON range of transdermal patches;
- addition of special warnings and precautions for use relating to application site skin reactions, allergic dermatitis and disseminated cutaneous hypersensitivity reactions;
- addition of a table showing the most common adverse effects observed during a clinical study conducted in patients suffering from dementia linked to Parkinson's disease and treated with the EXELON range of transdermal patches.

Change of 14 January 2013:
- addition of important administration instructions for the patients and their carers;
- addition of special warnings and precautions for use relating to misuse and error in doses, as well as dose adjustment in certain at risk populations;
- addition of the adverse effect: disseminated cutaneous hypersensitivity reactions (frequency not known) described in patients suffering from Alzheimer's disease treated with the EXELON range of transdermal patches during clinical studies.

09.3 Summary & discussion

The application for inclusion of this new dose (13.3 mg/24 hours) of the transdermal patch for the proprietary medicinal product EXELON is based on a study (OPTIMA) of 72 to 96 weeks, which comprised two periods: one open-label period of 24 to 48 weeks where all the patients received the same dose of EXELON (9.5 mg/24 hours); the other only in patients pronounced "decliners" at the end of 24 to 48 months of the open-label phase compared two doses of EXELON (9.5 mg/24 hours vs 13.3 mg/24 hours) for 48 weeks. The definition of decliner patients is based on functional decline gauged by the investigator and linked to a decrease of at least 2 or 3 points in the MMSE score (compared with that preceding the follow-up). The primary efficacy endpoints were cognition and autonomy, the secondary endpoints were behaviour (according to the Neuro Psychiatric Inventory), the period of onset of functional decline and cognitive test evaluating executive functions and attention. Cognition was evaluated according to the ADAS-Cog, a composite scale where the score varies from 0 to 70, exploring memory, language and executive functions. Functional autonomy was evaluated by the ADCS-ADL9, a composite scale evaluating capacity for basic activities of daily life as well as some instrumental activities. Its overall score varies from 0 to 78 and can be analysed on a subscale (basic activities: from 0 to 22, instrumental activities: from 0 to 56).

Results
The differences observed in the study endpoints, although statistically significant, do not show any clinical benefit relevant to the dose of 13.3 mg/24 hours compared with the dose of 9.5 mg/24 hours:

- As for cognition, the difference observed, at just 24 weeks, is low (1.3 points) bearing in mind that there is usually a difference of at least 4 points to evaluate whether there is any efficacy.
- As for functional autonomy, the differences at 24 weeks, from 1.7 to 2.3 points according to the analysis considered (LOCF or OC), have, at 48 weeks (2.2 or 2.5), questionable clinical relevance with a difference of less than 3 points on the ADCS-ADL scale (scored from 0 to 78).

The secondary efficacy endpoints (period of onset of functional decline, behavioural evaluation and performance in the executive test) did not differ between the two doses.

In the OPTIMA study, the adverse effects observed were in line with the safety profile known for rivastigmine. However, the digestive, psychiatric and nervous disorders were more common at a dose of 13.3 mg/24 hours than at a dose of 9.5 mg/24 hours. Considering the small increase in the dose of rivastigmine, the results of this study show a significant increase in adverse effects of rapid onset.

Furthermore, risks were added to the SPC, particularly that of application site skin reactions, allergic dermatitis and disseminated cutaneous hypersensitivity reactions (frequency not known).

Comments
The evaluated population, on the basis of the inclusion and non-inclusion criteria of patients for the open-label phase of this study (MMSE between 10 and 24, diagnosis of disease according to the DSM and the NINCDS-ADRA, etc.), has the same limits as that of the clinical trials conducted previously on Alzheimer's disease. The diversity of the clinical stage of the disease can result in different progressive declines in cognition which make interpreting the results difficult. The issue of the transferability of the results to an older population, and/or with a co-morbidity profile different from that of the included patients is also relevant here.
The differences observed in the study endpoints do not show any benefit that is clinically relevant to the dose of 13.3 mg/24 hours.
If using a high dose is justified, it begs the question as to what the benefit is of waiting 6 months to 1 year before offering it to the patient.
There is no study available comparing this medicinal product with another medicinal product in the symptomatic treatment of Alzheimer's disease.
The dose of EXELON 13.3 mg/24 hours exposes the patients to an increased risk of adverse effects (digestive, psychiatric, nervous disorders) compared with the dose of 9.5 mg/24 hours.

09.4 Planned studies

Risk Management Plan

As part of its marketing authorisation, the EXELON transdermal patches are subject to an RMP. The main points of the RMP are summarised in Table 7.

Table 6: Main points of the RMP of EXELON, transdermal patches.

Safety problem		Planned action
Identified major risks	Gastrointestinal disorders (nausea, vomiting, diarrhoea)	Routine pharmacovigilance activities, including a cumulative analysis in the PSUR
	Worsening of the motor symptoms linked to Parkinson's disease	
	Pancreatitis	
	Heart arrhythmias	
	Exacerbations of asthma and chronic obstructive pulmonary disease	
	Skin reactions and irritations at the application site	
	Hypertension	
	Gastrointestinal ulceration, bleeding and perforation	
	Epileptic seizures	
	Hallucinations	
	Syncope and loss of consciousness	
	Misuse of the medicinal product	Routine pharmacovigilance activities, including a cumulative analysis in the PSUR &
	Medication errors	

Safety problem		Planned action
		Specific monitoring of all spontaneous notifications, according to a predefined list of elements to be specifically monitored
	Dehydration	Routine pharmacovigilance activities, including a cumulative analysis in the PSUR
	Hepatic disorders	
	Severe skin reaction (bullous drug reactions)	
Potential major risks	Myocardial infarction	Routine pharmacovigilance activities, including a cumulative analysis in the PSUR
	Stroke	
	Pulmonary infections	
	Death	
	Acute renal failure	
	Missing important information	Not applicable

It should be noted that the risk of "severe skin reactions (bullous drug reactions)" listed first in the "major potential risks" category is from now on mentioned in the "identified major risks" category.
As part of the RMP, the EMA requested the conduct of a clinical study (CENA713D2409 study, the so-called DUS - Drug Utilization Study), the two main objectives of which are to evaluate inappropriate use of EXELON 13.3 mg/24 hours and the dose titration chart for EXELON transdermal patches. The protocol should be submitted to the EMA for validation in July 2013 and the final data submitted in December 2015 according to the information provided by the company.

010 THERAPEUTIC USE

Four medicinal products have, in France, received marketing authorisation (MA) in the symptomatic treatment of Alzheimer's disease.

- three acetylcholinesterase inhibitors (IAChE): ARICEPT (donepezil), REMINYL / REMINYL LP (galantamine) and EXELON (rivastigmine) indicated in "mild to moderately severe" Alzheimer's disease,
- an NMDA receptor antagonist: EBIXA (memantine) indicated in "moderate to severe" Alzheimer's disease.

Their efficacy, at best modest, is of questionable clinical relevance. It was demonstrated essentially on cognition and activities of daily life. No impact was demonstrated on the period of admission to an institution, the quality of life or morbidity and mortality. They can cause digestive, cardiovascular and neuropsychiatric adverse effects, thus necessitating discontinuation of the medicinal product. There is also a risk of drug interactions, particularly with the psychotropic drugs, often prescribed concomitantly.

In the absence of solid clinical data on the long-term effect of these medicinal products and owing to the uncertainty as to the relevance of clinical effects and the risk of serious adverse effects, their prescription is only based on considerations with a very low level of evidence.
At the mild stage of the disease, an acetylcholinesterase inhibitor (IAChE) can be used: donepezil, galantamine or rivastigmine. At the moderate to moderately severe stages, an IAChE (without favouring one over another) can be used. In these forms, the IAChEs represent an alternative to prescribing memantine. The advantage in administering rivastigmine as a transdermal patch compared with oral administration is questionable, as there is a risk of misuse, the consequences of which can be serious. At the severe stage, the anticholinesterase inhibitors do not have marketing authorisation. The advantage of combining two IAChE or one IAChE with memantine has not been demonstrated.

After 6 months of treatment, if the patient has reached the objectives set (for instance, stabilisation or slowing of cognitive decline) and in the absence of any serious adverse effect and/or any effect impairing the quality of life, the treatment may be continued for up to six further months.
If the efficacy has been maintained at 1 year, continuation of the treatment may be decided, after discussions with the carer, and if possible, the patient, following a multidisciplinary meeting

involving the treating doctor, geriatrician and neurologist or psychiatrist, in relation to the care network taking care of the patient.

The prescription of psychotropic drugs may sometimes be justified for as short a period as possible. Non-drug treatments (physical activity, stimulation, cognitive training) are also considered.

Use of the EXELON transdermal patch at a dose of 13.3 mg/24 hours
The benefit of this new dose of the EXELON transdermal patch is not clearly established, neither in its therapeutic use (when to prescribe and for which patients), nor as to how it compares with the dose of 9.5 mg/24 hours.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Alzheimer's disease represents a major public health burden in view of its high prevalence and incidence which, furthermore, are on the increase, the impact of this disease on loss of autonomy and mortality and its physical, psychological and financial repercussions on the family and friends of subjects. The burden remains major in the subpopulation of subjects suffering from mild to moderately severe Alzheimer's dementia.

◗ EXELON 13.3 mg/24 hours is a symptomatic treatment for mild to moderately severe Alzheimer's dementia.

◗ The efficacy/adverse effects ratio of the EXELON transdermal patch 13.3 mg/24 hours is low. The quantity of expected effects, compared with the EXELON 9.5 mg/ 24 hours dose, is at best low, of questionable clinical benefit and obtained at the price of a risk of onset of adverse effects (dose dependant) which may result in the treatment and its drug interactions having to be discontinued. Moreover, the provision of EXELON 13.3 mg/24 hours is likely to increase the occurrence of adverse effects by overdose already observed with EXELON transdermal patches which are given at lower doses (see RMP).

◗ In mild to moderately severe Alzheimer's disease, when the prescription of a medicinal product is decided, there are treatment alternatives to rivastigmine for these patients: donepezil, galantamine, other anticholinesterase drugs, and in moderate to moderately severe Alzheimer's dementia, memantine.

◗ The therapeutic use of EXELON 13.3 mg/24 hours is not clearly established compared with these alternatives.

◗ Public health benefit:
Alzheimer's disease represents a major public health burden in view of:
- high prevalence and incidence which, furthermore, are on the increase;
- the impact of this disease on loss of autonomy and mortality;
- its physical, psychological and financial repercussions on the family and friends of subjects.

The burden remains major in the subpopulation of subjects suffering from mild to moderately severe Alzheimer's disease.
Improvement in the overall treatment of Alzheimer's disease is a public health need which is an established priority (French Law on Public Health, AD plan 2008-2012).

During the re-assessment of 2011, the Committee had concluded that the "impact made by EXELON in real life on morbidity and mortality and quality of life remains to be seen:
- There is a question of whether the efficacy results can be transposed since the treatments have only been evaluated in clinical trials generally lasting only 6 months and where the presence of a carer was usually required.
- Data on public health criteria such as later admission to an institution, the transition to the next stage of severity, the burden on the carer or mortality are insufficient to conclude that they have a favourable impact. "
The data presented for EXELON 13.3 mg/24 hours do not allow the Committee to change this conclusion.
As a result, no public health benefit is expected for EXELON 13.3 mg/24 hours in the treatment of Alzheimer's disease.

Taking account of these points (poorly established efficacy, low effect size expected, the adverse effects most commonly expected, risk of overdose, existence of treatment alternatives), the Committee considers that the actual benefit of EXELON 13.3 mg/24 hours is insufficient in the indication "symptomatic treatment of mild to moderately severe Alzheimer's dementia" and at the dosage in the Marketing Authorisation for reimbursement by social security.

The Committee does not recommend inclusion of EXELON 13.3 mg/24 hours on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "symptomatic treatment of mild to moderately severe Alzheimer's dementia" and at the dosage in the Marketing Authorisation.

011.2 Improvement in actual benefit (IAB)

Not applicable.

011.3 Target population

Not applicable.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The conclusions of the Committee at the end of the re-assessment of medicinal products for the symptomatic treatment of Alzheimer's disease (October 2011) are unchanged, particularly concerning the need for re-assessing the benefit of continuing the prescription after 6 months of treatment and maintaining it after 1 year of treatment.