HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 January 2006

Xolair 150 mg, powder and solvent for solution for injection
Box containing one 150 mg bottle + one 2 mL ampoule of solvent (CIP: 370 225-7)

Applicant: Novartis PHARMA S.A.S.

Omalizumab

List I

Drug for initial hospital prescription on an annual basis only.
Initial prescription and renewal reserved for chest physicians or paediatricians.

Date of marketing authorisation (AMM): 25 October 2005

Reason for request: inclusion on list of drugs reimbursed by social security and for hospital use

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Omalizumab

1.2. Background

Omalizumab is a human monoclonal antibody that selectively binds to serum IgE. It belongs to a new pharmaco-therapeutic category for the treatment of asthma.

1.3. Indications

Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years and above) with severe, persistent, allergic asthma, who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80% of the theoretical value), as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled β2-agonist. Xolair treatment should only be considered for patients with convincing IgE-mediated asthma (see section 4.2 of the Summary of Product Characteristics).

1.4. Dosage

Use in adolescents and adults (12 years of age and older)
Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.
The appropriate dose and dosing frequency of Xolair is determined by baseline IgE (IU/mL) measured before the start of treatment, and by body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75–375 mg of Xolair in 1 to 3 injections may be needed for each administration.
Patients with IgE level lower than 76 IU/mL were less likely to benefit (see section 5.1 of the Summary of Product Characteristics). Prescribing physicians should ensure that patients with IgE below 76 IU/mL have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting treatment.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts.
Patients whose baseline IgE levels or body weight (kg) are outside the limits of the dosing table should not be given Xolair.
The maximum recommended dose is 375 mg omalizumab every two weeks.
For subcutaneous adminsitration only. Do not administer by intravenous or intramuscular route.
The injections are administered subcutaneously in the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.
There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare professional.

Table 1. Conversion from dose to number of vials, number of injections and total injection volume for each administration

Dose (mg)	Number of vials		Number of injections	Total injection volume (mL)
	75 mg[a]	150 mg[b]		
75	1[c]	0	1	0.6
150	0	1	1	1.2
225	1[c]	1	2	1.8
300	0	2	2	2.4
375	1[c]	2	3	3.0

[a] 0.6 mL = maximum delivered volume per 75 mg vial of Xolair
[b] 1.2 mL = maximum delivered volume per 150 mg vial of Xolair
[c] or use 0.6 mL taken from a 150 mg vial of Xolair

Table 2. ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks

	Body weight (kg)									
Baseline IgE (IU/ml)	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3	
>200–300	150	150	225	300	300					
>300–400	225	225	300							
>400–500	225	300								
>500–600	300	300								
>600–700	300									

Table 3. ADMINISTRATION EVERY 2 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 2 weeks

	Body weight (kg)									
Baseline IgE (IU/ml)	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30–100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
>100–200									225	300
>200–300						225	225	225	300	375
>300–400				225	225	225	300	300		
>400–500			225	225	300	300	375	375		
>500–600			225	300	300	375	DO NOT ADMINISTER – data is unavailable for dose recommendation			
>600–700		225	225	300	375					

Treatment duration, monitoring and dose adjustments:
Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms.
At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are adminsitered. The decision to continue Xolair treatment should be based on whether a marked improvement in overall asthma control is seen (see section 5.1: Physician's overall assessment of treatment effectiveness).

Total IgE can be elevated during treatment and can remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose detemination if treatment with Xolair has been interrupted for one year or more.
Doses should be adjusted for significant changes in body weight (see Tables 2 and 3).

Elderly (65 years of age and older):
There are limited data available on the use of Xolair in patients older than 65 years, but there is noevidence that elderly patients require a different dosage from younger adult patients.

Children (aged below 12 years):
Safety and efficacy of Xolair in paediatric patients below the age of 12 years have not been established and use of Xolair in such patients is therefore not recommended.

2 SIMILAR MEDICINAL DRUGS

2.1. ATC classification (2005)

R	Respiratory system
R03	Drugs for obstructive airway diseases
R03D	Other systemic drugs for obstructive airway diseases
R03DX	Other systemic drugs for obstructive airway diseases
R03DX05	Omalizumab

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Xolair is the only drug in its therapeutic category.

2.2.2 Comparisons that have been carried out

Not applicable.

2.3. Medicines with a similar therapeutic aim

Alternative drugs used to treat severe, persistent asthma are: inhaled corticosteroids, long-acting bronchodilators, prolonged-release theophylline and oral and systemic corticosteroids.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Seven trials have been submitted in support of the application including:

- 5 parallel-group trials comparing omalizumab to placebo in combination with the standard treatment;
- 2 open trials comparing omalizumab to placebo both in combination with the standard treatment.

Only one study, described below, has been performed in patients with the validated indication, i.e. with severe, persistent, allergic asthma, inadequately controlled despite daily, high-dose inhaled corticosteroid therapy combined with a long-acting, inhaled ß$_2$-agonist.

Aim of the trial: to compare over 28 weeks the efficacy of omalizumab with placebo as an add-on therapy to high-dose inhaled corticosteroid therapy and long-acting β_2-agonist.

Method: multicentre double-blind randomised controlled study.

Population studied: 419 adult and adolescent patients over 12 years old with severe persistent asthma, which was inadequately controlled despite treatment, equivalent to step 4 of the GINA[1] guidelines.

Eligible patients had impaired lung function (40% $\leq FEV_1 <$80% of predicted normal value, FEV_1 reversibility $\geq$12% 30 minutes after salbutamol administration), total serum IgE levels between 30 and 700 IU/Ml and a positive skin prick test to at least one perennial allergen.

Despite long-term treatment with a high-dose inhaled corticosteroid combined with a long-acting bronchodilator:

- asthma symptoms were inadequately controlled;
- patients had experienced at least two distinct asthma exacerbations severe enough to require systemic corticosteroid therapy or one severe exacerbation resulting in hospitalisation or treatment in an emergency department during the previous 12 months, despite regular treatment with a high-dose, inhaled corticosteroid and by long-acting β_2-agonist.

Treatments:
2 patient groups:

- omalizumab (N=209)
- placebo (N=210)

Posology: 1 administration every 2 to 4 weeks of a dose determined by body weight and total serum IgE levels.

[1] GINA : Global Initiative for Asthma

All patients received, in addition, a long-acting ß$_2$-agonist and inhaled corticosteroid therapy at a mean daily dose equivalent to 2.330 µg beclomethasone dipropionate.

Patients were permitted to take anti-asthma drugs in addition to inhaled corticosteroids and long-acting β_2-agonists on condition that these additional treatments had been started at least 4 weeks before randomisation.. Patient randomisation was stratified according to initial treatment.

Endpoints:

- primary endpoint: rate of clinically significant asthma exacerbations[2]. A clinically significant asthma exacerbation was defined as a worsening of asthma symptoms severe requiring oral or intravenous corticosteroid treatment.
- secondary endpoints: severe exacerbation rate (defined in accordance with the GINA recommendations by PEF or FEV_1 < 60% of personal best), number of emergency visits, global quality of life score measured using the Juniper Asthma Quality of Life questionnaire, PEF, FEV_1.

Amendments to the protocol:

- Because of the differences in severity noted retrospectively between the omalizumab and placebo groups, Poisson regression with adjustments for the exacerbation rate during the 14 months prior to inclusion was used for analysis of the primary endpoint. This was in addition to the adjustments made for the drug administration schedule, centres classified by country and previous anti-asthma treatment.
- A total of 482 patients had initially been included in the trial. Analysis of the results was conducted on the intention-to-treat population included after the most significant amendment to the protocol (on 419 patients), which changed the inclusion criteria. This was a change made after the GINA guidelines were updated in 2002 to the dose level of inhaled corticosteroid at which patients were classified as being at the severe, persistent stage.

Results:

Severity of asthma on inclusion in the study:

Patients had had allergic asthma for more than 20 years on average. The majority of patients had at least 4 perennial allergies and more than half had a seasonal allergic manifestation.

FEV_1 (as % of predicted normal value) was 61% in both groups. Serum IgE was 197.6 IU/mL in the omalizumab group and 189.6 IU/mL in the placebo group.

Patients in the omalizumab groups had more severe asthma than those in the placebo group, particularly in terms of exacerbation rate during the 14 months prior to inclusion (see table below).

[2] Attribution applied to the primary endpoint only: the addition of one exacerbation to the number of asthma exacerbations observed for a patient who had stopped the trial prematurely unless the patient in question had one asthma exacerbation during the 7 days prior to stopping the trial prematurely.

History of the disease: main characteristics during the 14 months prior to inclusion

	Omalizumab N=209	**Placebo N=210**
Hospitalisation – n (%)	83 (39.7)	79 (37.6)
Admission to intensive care – n (%)	22 (10.5)	19 (9.0)
Admissions to emergency department – n (%)	118 (56.5)	116 (55.2)
Need for ventilatory support – n (%)	29 (13.9)	13 (6.2)
One of the above 4 events (increased risk of death from asthma) - n (%)	143 (68.4)	136 (64.8)
Number of visits to hospital emergency department		
Mean (standard deviation)	1.68 (2.61)	1.48 (2.47)
Number of emergency medical consultations		
Mean (standard deviation)	4.9 (5.66)	4.9 (6.11)
Absence (from school/work) number of days		
Mean (standard deviation)	27.7 (48.59)	34.0 (58.53)
Classification of patients according to the number of exacerbations during the 14 months prior to randomisation - n (%)		
Exacerbations		
0	2 (1.0)	0
1	31 (14.8)	32 (15.2)
2	90 (43.1)	100 (47.6)
3	47 (22.5)	55 (26.2)
4	19 (9.1)	13 (6.2)
5	11 (5.3)	5 (2.4)
6	4 (1.9)	3 (1.4)
7	3 (1.4)	2 (1.0)
9	1 (0.5)	0
14	1 (0.5)	0
Number of exacerbations	551	506

Primary endpoint:

Analysis without adjustment for exacerbation rate before treatment did not demonstrate any significant difference between treatments (0.74 exacerbation/patient on omalizumab versus 0.92 on placebo).

After adjustment of the data according to baseline rate, the rate of clinically significant exacerbations during the 28 weeks of treatment was significantly lower on omalizumab than on placebo (0.68 exacerbation/patient versus 0.91 or a difference of 0.23 exacerbation/patient). This difference is equivalent to 1 exacerbation prevented every 2 years and is clinically meaningful.

Secondary endpoints:

The rate of severe exacerbations of asthma (see table below) per patient was significantly reduced during the 28 weeks in the omalizumab group compared with the placebo group (0.24 versus 0.48 exacerbation/patient or a difference of 0.24 exacerbation/patient).

Severe exacerbation rate/patient and distribution of patients by exacerbation rate (analysis without attribution)

	Omalizumab (N=209)	Placebo (N=210)	p
Number of severe exacerbations	49	100	
Number of severe exacerbations/ patient	**0.24**	**0.48**	**0.002**
Number (%) of patients with at least one severe exacerbation	35 (16.8)	55 (26.2)	
Number (%) of patients with:			0.008
0 severe exacerbation	174 (83.3)	155 (73.8)	
1 severe exacerbation	26 (12.4)	31 (14.8)	
2 severe exacerbations	6 (2.9)	11 (5.2)	
3 severe exacerbations	1 (0.5)	5 (2.4)	
4 severe exacerbations	2 (1.0)	8 (3.8)	

The total number of emergency visits (see table below) was significantly lower in the omalizumab group than the placebo group (0.24 emergency visits/patient versus 0.43). Emergency visits included all hospitalisations, emergency department consultations and unscheduled visits to the doctor.

Emergency visit rate and distribution of patients according to emergency visit rate (analysis without attribution)

Type of visit	Omalizumab (N = 209) n (%)	Placebo (N = 210) n (%)	p
Number of emergency visits/ patient	**0.24**	**0.43**	**0.038**
Number (%) of patients with:			
0 emergency visit	176 (84.2)	168 (80.0)	
1 emergency visit	24 (11.5)	21 (10.0)	
2 emergency visits	4 (1.9)	9 (4.3)	
3 emergency visits	3 (1.4)	7 (3.3)	
≥ 4 emergency visits	2 (1.0)	5 (2.4)	

The proportion of patients whose improvement was statistically significant and clinically meaningful (≥ 0.5), in terms of global quality of life score measured using the validated Juniper questionnaire, was significantly higher on omalizumab than on placebo (60.8% versus 47.8%, p=0.008).

Morning PEF improved compared with placebo. The improvement, although significant, was not clinically meaningful, with a difference of 11 L/min in favour of omalizumab at the end of the study.

FEV_1 improved significantly compared with placebo: 190 mL on omalizumab versus 96 mL on placebo. The inter-group difference (94 mL) is not clinically meaningful. However, the % of patients whose FEV_1 improved by more than 200 mL was greater on omalizumab (28% vs. 13.8%).

Comments:

- It was unfortunate that the study was performed over 28 weeks only. As the rate of severe exacerbations was low in the majority of patients (no severe exacerbation occurred during the study in 73.8% of patients on placebo), 12 months' duration would have been more appropriate.

- Furthermore, the results for exacerbation rate should be interpreted with caution insofar as asthma severity was markedly more pronounced before the study for all patients. In fact all patients in the group intended to receive placebo had experienced at least 1 exacerbation during the 14 months preceding the study and 89% of patients had experienced between 1 and 3 exacerbations, whereas 73.8% had no exacerbations during the trial and only 22.4% had between 1 and 3 exacerbations.

3.2. Undesirable effects/Safety

The most commonly reported undesirable effects (>1/100; <1/10) were reactions at the injection site (pain, rash, redness and pruritus), headaches and fatigue. Most of these undesirable effects were mild to moderate in intensity.

Rare cases of cancer were reported during the clinical trials (<1/100). Incidence was slightly higher in the omalizumab group [25 cancers out of 5015 patients (0.5%)] than in the placebo group, [5 cancers out of 2,854 patients (0.18%)]. The variation in types of cancer observed, the relatively short exposure time and the clinical characteristics of each individual case make a cause-effect relationship very unlikely. The overall incidence rate of cancers for omalizumab in the programme of clinical trials was comparable to that in the general population. However, an increased cancer rate in patients undergoing long-term treatment with omalizumab cannot be excluded. The risk management plan validated by EMEA will supply long-term data.

3.3. Conclusion

A pilot study in the form of a randomised, double-blind, multicentre study compared the efficacy of omalizumab with that of placebo in a population of 419 patients with severe persistent allergic asthma (40% ≤ FEV_1 <80% of predicted normal values, reversibility of FEV_1 ≥12% and total serum IgE of 30 and 700 UI/mL with a positive skin prick test to at least one perennial allergen).

After 28 weeks of treatment and adjustment for imbalance in baseline exacerbations, omalizumab significantly reduced the rate of clinically significant exacerbations (worsening of asthma necessitating either oral or intravenous corticosteroid therapy) compared to placebo: 0.68 exacerbation/patient on omalizumab versus 0.91 on placebo, that is a difference of 0.23 exacerbation/patient, which is equivalent to 1 exacerbation prevented every 2 years.
A reduction of similar magnitude, which was also statistically significant, was obtained on severe exacerbation rate defined by a PEF or FEV_1 <60% of best personal (0.24 severe exacerbation/patient or 1 severe exacerbation prevented every 2 years) and on the number of emergency visits (0,19visits/patient).
These effects can be considered to be moderate.

The proportion of patients who had a clinically meaningful improvement (≥ 0.5) in global quality of life score according to the validated Juniper questionnaire was significantly greater on omalizumab than on placebo (60.8% versus 47.8%).

The improvements noted in PEF and FEV_1 compared to placebo, although statistically significant, are not clinically meaningful (+11 L/min for morning PEF and +94 mL for FEV_1).
It has not been established whether efficacy is maintained beyond 28 weeks.

The safety data showed that omalizumab was well tolerated. The most commonly reported undesirable effects were reactions at the injection site, fatigue and headaches. In the long term, an increased cancer rate cannot be excluded. The risk management plan validated by EMEA will supply long-term data.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Atopic asthma occurs in 70% to 80% of asthmatic adults and in 95% of asthmatic children. Severe, persistent asthma, when inadequately controlled, exposes patients to severe exacerbations which result in hospitalisations or treatment in an intensive care unit and may be life-threatening.

This medicinal product is classified as a disease-modifying treatment.

Benefit to public health

In terms of public health asthma represents burden. The sub-population of patients who could benefit from Xolair (patients with severe, persistent, allergic asthma which is inadequately controlled) represents a small burden.

While a therapeutic need does exist, available data do not confirm that the medicinal product Xolair is capable of responding to this need.

When the data obtained in clinical trials (results at the threshold of significance, no saving in corticosteroids demonstrated) and the available alternatives are considered, it is not expected that this medicinal product will have any impact in terms of morbidity and mortality.

Furthermore, it is still unclear whether the results of trials can be extrapolated because there is still some uncertainty about whether this subcutaneous treatment can be maintained and even about its long-term safety.

As a result no public health benefit is expected for the medicinal product Xolair.

The ratio of efficacy to undesirable effects for this medicinal product is moderate.

This medicinal product is reserved for adult and adolescent patients (12 years and above) with severe, persistent, allergic asthma (assay of IgE required), which is inadequately controlled by standard treatments: inhaled high-dose corticosteroids and long-acting β2 agonists.

There are no alternatives from the same therapeutic category.

The actual benefit from Xolair 150 mg is substantial.

4.2. Improvement in actual benefit

The improvement in actual benefit from Xolair is minor (level IV) in the standard management of patients with severe, allergic asthma inadequately controlled by inhaled, high-dose corticosteroid therapy plus a long-acting β_2 agonist.

4.3. Therapeutic use

4.3.1. Standard disease management

The standard treatment for severe, persistent asthma is a high-dose, inhaled corticosteroid combined with maintenance treatment with a bronchodilator in the form of an inhaled, long-acting β_2 agonist.
If asthma remains inadequately controlled, despite the combination of a high-dose, inhaled corticosteroid with an inhaled, long-acting β_2 agonist, the next step is normally an add-on treatment consisting of a short course or maintenance treatment with oral corticosteroids. Regular attempts should then be made to reduce the level of treatment or to discontinue it.

4.3.2 Therapeutic use of the medicinal product

Omalizumab, a monoclonal anti-IgE antibody, is the first representative of a new pharmaco-therapeutic category. Its place in the disease management is as add-on therapy in patients with severe, persistent asthma, allergic in origin and inadequately controlled by inhaled, high-dose corticosteroid therapy and an inhaled long-acting β_2 agonist.

Omalizumab is an alternative to oral corticosteroid therapy. No study has been able to demonstrate that omalizumab makes it possible to reduce the use of oral corticosteroids.

Inadequately controlled asthma is defined by:
- reduced lung function (FEV_1 <80% of the theoretical value)
- frequent diurnal symptoms and nocturnal awakenings and
- severe, multiple and documented asthma exacerbations.

Omalizumab is restricted to adult and adolescent patients over 12 years of age.

Treatment should be initiated after compliance with the initial treatment has been confirmed or after attempts to improve compliance have been made.

The allergic origin of the asthma should be confirmed by means of a skin prick test or positive RAST to a perennial aeroallergen. Before starting treatment, patients' IgE level should be measured by one of the available methods for assay of total serum IgE level in order to calculate the appropriate dose. Only patients whose total serum IgE is between 30 and 700 UI/mL and whose weight is included in the dosing tables in the SPC can be treated with omalizumab.

Treatment efficacy should be evaluated after 16 weeks before treatment is continued.

4.4. Target population

The target population for Xolair is defined as patients with severe persistent allergic asthma inadequately controlled by inhaled corticosteroid treatment combined with an inhaled long-acting β_2 agonist, and whose total serum IgE is between 30 and 700 UI/mL and whose weight is included in the dosing tables in the SPC.

There are two available sources for estimating the prevalence of severe, persistent asthma:

- data from CREDES[3] (2002).

  According to this source the prevalence of severe persistent asthma is 0.4% for the population aged 12-49 years and 1% for the population aged 50 years and above, which, related to the French population (data from INED 2004), represents 124 000 people aged

[3] CREDES: Centre for Health Economics Research, Study and Documentation

12-49 years and 206 000 people aged 50 years and above to give a total of 330 000 people.

- an epidemiological study (PREVAS study) carried out by the company in patients treated by 118 lung and allergy specialists. This study cannot be used to estimate the prevalence of severe asthma because it contains methodological inadequacies. The doctors involved were poorly representative and response rate was low (118 responses out of 955 doctors interviewed). In addition it has not been published.

As a result the CREDES data will be used to estimate the prevalence of severe asthma and the PREVAS study, despite its inadequacies, will be used to estimate the proportion of patients who are inadequately controlled.
Thus, the PREVAS study estimates the proportion of patients with severe, persistent, inadequately controlled asthma to be 40% of patients with severe, persistent asthma, which, when extrapolated to the population with severe asthma in the CREDES study, is equivalent to 132 000 people.

The proportion of patients with allergic asthma is between 70 and 80% of adults (Asthma management and prevention programme, 2002-2005, Ministry of Solidarity, Health and the Family). This puts the estimated population of severe, persistent, allergic asthma patients at between 92 000 and 105 000 people.

The CREDES study is based on self-reported data, which means there is a substantial risk of overestimation.
On the hypothesis that this overestimation is in the order of 50%, the population of patients with severe, persistent, allergic asthma is in the order of 46 000 persons.

However, according to the experts, only those patients with total serum IgE levels between 30 and 700 UI/mL and a weight included in the dosing tables should be used.
On this basis the target population for Xolair is likely to be in the order of 10 to 20 000 patients.

4.5. Transparency Committee guidelines

Approval for inclusion on the list of reimbursable medicinal products and on the list of medicinal products approved for use by hospitals and various public services.

The committee expects to re-evaluate the actual clinical benefit of the medicinal product on the basis of the results of studies provided for in the risk management plan, in particular in relation to long-term safety, and requests that a specific study be set up in patients treated with Xolair.
The aim of this study will be to describe the conditions of use for this medicinal product under actual treatment conditions, in particular,
- the conditions for initiating treatment (profile of patients treated, including age and indication criteria in the MA, previous treatments etc.),
- concomitant therapy,
- duration of treatment.

Reasons should be given for the duration of the study as determined by a scientific committee. Duration should be long enough to meet the Committee's requirements.

4.5.1 Packaging: suitable for conditions of prescription and supply.

4.5.2 Reimbursement rate: 65 %