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Cost-effectiveness of GRAZAX[®] for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe

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Received 14 September 2006; accepted 2 May 2007

KEYWORDS

Rhinoconjunctivitis;
Grass pollen allergy;
Allergen specific
immunotherapy;
Grass allergen tablet;
Cost-effectiveness;
QALY

Summary

Background: Allergic rhinoconjunctivitis is a global health problem. Around 14 million people in Spain, France, Italy, and Austria suffer from grass pollen induced allergic rhinitis. Standard care only provides symptoms relief, while allergen specific immunotherapy (SIT) treats the underlying cause of the disease. Grazax[®] from ALK-Abelló is a new, tablet-based, effective route of SIT for home treatment. The objective was to assess the cost-effectiveness of Grazax[®] in four Southern European countries.

Methods: A prospective pharmacoeconomic analyses was carried out alongside a multi-national, clinical trial measuring the efficacy of Grazax[®]. Pooled data on resource use and health outcomes were collected. A societal perspective was adopted, and the analysis had a nine-year time horizon. The primary outcome measure was quality adjusted life years (QALYs).

Results: Grazax[®] was superior to standard care for all efficacy endpoints, including QALYs gained, and resulted in significantly less use of rescue medication and fewer hours missed from work. Grazax[®] was cost-effective for all countries for an annual price in the range of €1500–€1900. The result was improved by inclusion of future costs of asthma and exclusion of Spanish trial centers which experienced an exceptionally low pollen season.

Conclusion: The analysis illustrates that allergen SIT with Grazax[®] for grass pollen induced rhinoconjunctivitis is a cost-effective intervention in Southern Europe.

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Introduction

Allergic rhinoconjunctivitis is a very common, global health problem.¹ Numerous studies have shown a dramatic increase in the disease prevalence in recent decades. While the

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prevalence of allergic rhinitis is believed to have been in the order of 1% in the beginning of the 20th century,² an average adult prevalence of allergic rhinitis between 17.8% and 26.0% was found in European countries in 2004 with approximately 52% of these patients suffering from grass pollen induced rhinitis.³ This means that around 12% of the adult population in Europe suffer from grass pollen induced allergic rhinitis. For the Southern European countries—Spain, Italy, France, and Austria, which are in focus in the present study, this amount to nearly 14 million people. When looking at the future prevalence of allergic rhinitis the economic burden of the disease becomes even more evident. A recent survey projects that one out of two children will have allergic rhinitis in 2020.⁴

The increase in the occurrence of allergic rhinitis is paralleled by similar increases in other allergic disorders such as eczema and asthma, and several studies have shown that asthma and allergic rhinitis often co-exist in the same patients.^{1,5,6} It has been estimated that asthma affects approximately 38% of patients diagnosed with allergic rhinitis⁷ and among patients diagnosed with asthma, 60–78% have allergic rhinitis.⁸

The goal of symptomatic treatment is to reduce the symptoms, both in severity and duration. The most commonly used symptomatic medications in Europe are antihistamines, corticosteroid nasal spray and eye drops.⁹ As symptomatic medication is solely used for the relief of symptoms and has no long-lasting effect, allergic patients may require life-long symptomatic medication.

As opposed to symptomatic medication allergen specific immunotherapy (SIT) treats the underlying course of the allergic disease and offers a long-lasting preventive effect.¹⁰ A large number of randomized controlled trials have documented symptomatic relief as well as the beneficial and long-lasting preventive effect of SIT.^{11–18} In Spain and Austria SIT has predominantly been delivered by subcutaneous injections, while in France (75%) and Italy (70%) sublingual immunotherapy is the most widespread route of administration (unpublished data). For optimal effect the WHO recommends that SIT should be given over a period of at least three years.^{10,19}

Grazax[®] from ALK-Abelló is a new, registered, tablet-based SIT product against allergic rhinoconjunctivitis, for home administration. Daily intake of Grazax[®] should start at least eight weeks prior to the grass pollen season.

The improved clinical efficacy and resource utilization patterns associated with the practice of SIT have cost implications for the health care sector and the society in general. For authorities to decide how to spend the resources within the health care sector in an optimal way, prospective cost-effectiveness analyses conducted alongside clinical trials of a certain size are needed. Attempts have been made to assess the cost implications for sublingual immunotherapy,^{20–22} but the present analysis is to our knowledge the first study that analyses the cost-effectiveness of sublingual immunotherapy prospectively and according to guidelines for pharmacoeconomic evaluation.

The objective of the present study was therefore to assess the cost-effectiveness of Grazax[®] compared with symptomatic medication against grass pollen induced rhinoconjunctivitis. This pharmacoeconomic analysis was carried out for a group of four Southern European countries — Spain,

Italy, France, and Austria. These countries were chosen, because of the perception of the burden of allergic rhinitis was assumed to be uniform across the four countries, and because of similarities in costs, treatment patterns and health care systems.

Methods

The pharmacoeconomic analysis was designed as cost-effectiveness and cost-utility analyses. Prospective data on resource use and quality of life (QoL) was collected alongside a clinical phase III trial which was part of the largest clinical development programme that has been undertaken for a SIT product, including more than 1700 patients.^{23–25} The trial was conducted as a multinational trial including eight countries (Austria, Denmark, Germany, Italy, The Netherlands, Spain, Sweden, and United Kingdom). The trial included 634 patients where 316 patients were randomized to the Grazax[®] arm and 318 patients to the placebo arm. The average age was 34 years (Table 1).²⁶ Inclusion criteria in the trial were: 18–65 years old; at least 2-year clinical history of significant grass pollen induced allergic rhinoconjunctivitis; specific IgE against *Phleum pratense* CAP class 2; positive skin prick test against *Phleum pratense*, wheal diameter 3 mm; and FEV1 higher than 70% of predicted value.²⁶

Grazax[®] was compared to standard care, i.e. symptomatic medication against grass pollen induced rhinoconjunctivitis using the placebo alternative of the trial. This

Table 1 Demography of the patients in the clinical trial

	Grazax [®]	Placebo
Total number of subjects (N)	316	318
Sex		
Men/Women	57%/43%	61%/39%
Age (years)		
Mean (standard deviation)	33.8 (9.6)	34.5 (10.0)
Country		
Austria	4%	4%
Denmark	19%	19%
Germany	24%	24%
Italy	11%	11%
Netherlands	6%	7%
Spain	8%	7%
Sweden	10%	10%
United Kingdom	18%	19%
Grass pollen allergy (severity)		
Moderate/Severe	43%/57%	45%/55%
Grass pollen allergy (years)		
Mean (standard deviation)	15.9 (9.8)	15.7 (10.4)
Median	14.0	14.5

Source: Dahl et al.²⁶

was possible as both study arms were allowed symptomatic medication, which made it possible to model the placebo arm as standard care. This has implications which are discussed later in the discussion section. Following the different national guidelines for pharmacoeconomic evaluation in the countries considered, a societal perspective focusing on both the direct health care costs and indirect costs in the form of productivity losses due to allergic rhinoconjunctivitis was adopted.^{27–30}

Due to the relatively small number of patients from the centers in Spain, Italy, and Austria, the data on resource use and QoL from all 634 patients in the trial were analyzed in a pooled manner.^{26,31} However, country-specific unit costs from each of the four countries considered were used.

Resource use, as well as unit costs (partly), was identified before the randomization code of the trial was broken. The resource use data collected included visits to the physician and acute ward visits, symptomatic medication, asthma medication, eventual hospitalization, and hours missed from work due to allergic rhinitis. During the trial period, patients were allowed to use clearly defined rescue medication against rhinitis (i.e. loratadine and budesonide), and asthma (i.e. salbutamol and fluticasone) dispensed according to protocol criteria. This concomitant medication was confirmed by country-specific experts in allergy to be relevant for patients in the four countries considered, although it was more limited than in real practice.

Use of symptomatic medication was recorded by the patients on a daily basis in diaries, whereas visits to

physicians and hours missed from work were recorded in weekly diaries during the pollen season. Besides the physician visits collected in the weekly diary, the literature was searched to determine the annual number of physician visits for a patient that has not undergone immunotherapy. A recent European survey found this to be between 2.7 and 5.1 visits in the four Southern European countries considered.⁹ These literature-based visits were added to the analysis. Resource use only associated with the trial per se (protocol driven costs) such as visits for monitoring purposes was not included in the pharmacoeconomic analysis,³² as these costs would not occur in a real life setting, which the analysis should represent.

Unit costs represent the values assigned to the consumed resources.³² In each of the four countries, country-specific unit costs were identified and used in the valuation of the resource use data. These unit costs were official tariffs, retail drug prices (pharmacy selling prices), average wage rates from national statistics bureaus, etc. (Table 2). All unit costs were in Euro (2005) were possible.

Discounting

In accordance with the guidelines for pharmacoeconomic analyses in the countries assessed, all future costs and health effects were discounted at rates between 3% and 5% depending on the country. Discounting is a method used to adjust future costs and benefits to their present value, i.e.

Table 2 Unit costs applied from the four countries (2004–2005 prices, Euros)

	France	Italy	Spain	Austria
General practitioner (per office visit) ^a	22.00	13.00	27.50	16.74
Allergy specialist (per office visit) ^b	27.00	18.00	54.44	7.73
Accident & emergency (per visit) ^c	47.10	302.12	102.39	270.00
Loratadine, 10 mg (per tablet) ^d	0.47	0.64	0.21	0.34
Budesonide, 50 mcg (per dose) ^e	1.67	0.07	0.04	0.19
Prednisone, 5 mg (per tablet) ^f	0.10	0.15	0.25	0.52
Salbutamol, 200 mcg (per dose) ^g	0.14	0.22	0.04	0.23
Fluticasone, 250 mcg (per dose) ^h	0.38	0.53	0.14	0.68
Production loss (average salary/h) ⁱ	27.70	20.00	14.21	17.33

^aFrance: Service-Public, <http://www.service-public.fr/>. Italy: Degli et al.³⁴ Spain: Lindgren et al.³⁵ Austria: Expert advice.

^bFrance: Service-Public, <http://www.service-public.fr/>. Italy: Pinotti et al.³⁶ Spain: Sera-Batles et al.³⁷ Austria: Expert advice.

^cFrance: Van Ganse et al.³⁸ Italy: ERMES, <http://www.regione.emilia-romagna.it>. Spain: Lindgren et al.³⁵ Austria: Expert advice.

^dFrance: Clarityne, 15 tablets (L'Assurance Maladie, www.codage.ext.cnams.fr). Italy: Fristamin, 7 tablets (Federfarma, <https://www.federfarma.it>). Spain: Ratiopharm, 20 tablets (www.portalfarma.com/www.vademecom.medicom.es). Austria: Acris, 7 tablets (Omni medical center, www.omc24.at).

^eFrance: Budesonide Arrow, 20 doses (L'Assurance Maladie, www.codage.ext.cnams.fr). Italy: Aircort Spray Nas, 200 doses (Federfarma, <https://www.federfarma.it>). Spain: Aldo-Union, 200 doses (www.portalfarma.com/www.vademecom.medicom.es). Austria: Pulmicort Topinasal, 120 doses (Omni medical center, www.omc24.at).

^fFrance: Prednisone Arrow, 30 tablets (L'Assurance Maladie, www.codage.ext.cnams.fr). Italy: Deltacortene, 10 tablets (Federfarma, <https://www.federfarma.it>). Spain: Dacortin, 30 tablets (www.portalfarma.com/www.vademecom.medicom.es). Austria: Galen, 20 tablets (Omni medical center, www.omc24.at).

^gFrance: Ventodisk, 56 doses (L'Assurance Maladie, www.codage.ext.cnams.fr). Italy: Ventolin Diskus inal, 60 doses (Federfarma, <https://www.federfarma.it>). Spain: Aldo-Union, 200 doses (www.portalfarma.com/www.vademecom.medicom.es). Austria: Cyclo-caps, 60 doses (Omni medical center, www.omc24.at).

^hFrance: Flixotide Diskos, 15 doses (L'Assurance Maladie, www.codage.ext.cnams.fr). Italy: Flixotide Diskus, 60 doses (Federfarma, <https://www.federfarma.it>). Spain: Inalacor, 120 doses (www.portalfarma.com/www.vademecom.medicom.es). Austria: Artemur, 60 doses (Omni medical center, www.omc24.at).

ⁱFrance, Italy and Spain: Eurostat, <http://epp.eurostat.cec.eu>, Austria: Statistik Austria.

the future resource use cost and benefit streams are reduced or 'discounted' to reflect the fact that resources spent or saved in the future should not weigh as heavily in programme decisions as resources spent or saved today, due to positive time preferences.³² The term positive time preference refers to the fact that individuals value one Euro today more than one Euro received a year from now.

Duration of the analysis

A crucial point in the model used in this cost-effectiveness analysis is the assumption on the sustained effect of SIT with Grazax[®]. Based on results from current SIT treatment it is assumed that after three years of treatment with Grazax[®], there will be an additional sustained effect for six additional years. As a consequence the prospective data from the clinical trial is extrapolated into a nine-year time horizon by linear extrapolation as outlined in Fig. 1.

Several studies have documented a sustained effect of injection SIT up to seven years after the treatment has been finalized.^{14,16–18,33} This sustained effect has also been documented for the sublingual route of administration.¹⁵

Based on the evidence above we have used a nine-year time horizon in this analysis — assuming six years of sustained effect after treatment with Grazax[®] is finalized. The assumption on six years of sustained effect has been documented in studies where patients have been treated with SIT containing the same active ingredient as works in Grazax[®].^{14,33} Any sustained effect past the six years which is assumed in the model will further strengthen the overall cost-effectiveness result.

Impact of allergic asthma

As presented in the Introduction, patients with allergic rhinitis often also experience symptoms of asthma.^{7,8} This has been shown both for children and adults.^{16,39} An additional benefit of SIT is that it reduces the risk of developing allergic asthma later in life. This preventive effect has previously been demonstrated for subcutaneous immunotherapy in children.^{16,17} Only 24% of patients treated with SIT developed asthma within three years compared with 44% of the patients treated with conventional pharmacotherapy — standard care with antihista-

mines.¹⁶ Similar results have been demonstrated for sublingual immunotherapy.⁴⁰

Assuming that this evidence was transferable to tablet-based immunotherapy, the future costs related to asthma was included in the country-specific cost-effectiveness analyses of Grazax[®] as a sensitivity analysis. This was done in each of the four Southern European countries by identifying existing country-specific costs and cost of illness studies, which had estimated the annual direct health care costs of asthma as well as the annual production loss due to asthma.^{37,38,41,42} The cost figures for Austria due to asthma were taken from a German study as no Austrian study was present.⁴² Based on this evidence the annual direct and indirect health care costs per asthma patient were calculated and included in the cost-effectiveness analysis. The risk of developing asthma was then included in the cost-effectiveness analysis by assigning weights to the risk corresponding to the result from Möller et al.¹⁶

Statistics

A common feature of resource use data is that they are positively skewed, because costs are naturally bounded by zero, i.e. patients with zero utilization, and because costs have no logical upper bound, i.e. outlier patients with very high costs.³² This was also the case in the trial. Performing statistical analyses such as *t*-tests standard assumptions of normal distributions are not appropriate in these situations, why a logarithmic transformation of $\log(R_i+1)$ was used to make the distribution more normally distributed.⁴³

Quality of life

Quality adjusted life years (QALYs) measure the patients' health-related QoL on a scale from zero (dead) to one (perfect health), and are a multi-attribute utility scale that can generate a single numeric index of health related QoL.^{44,45} Validated, country-specific versions of the commonly used EuroQol-5D (EQ-5D) instrument was used to measure QALYs in each of the countries participating in the trial. EQ-5D describes the patients' QoL using five dimensions — mobility, self-care, usual activities, pain/discomfort and anxiety/depression.³² Each of these dimensions are divided into three levels of severity indicating no problems,

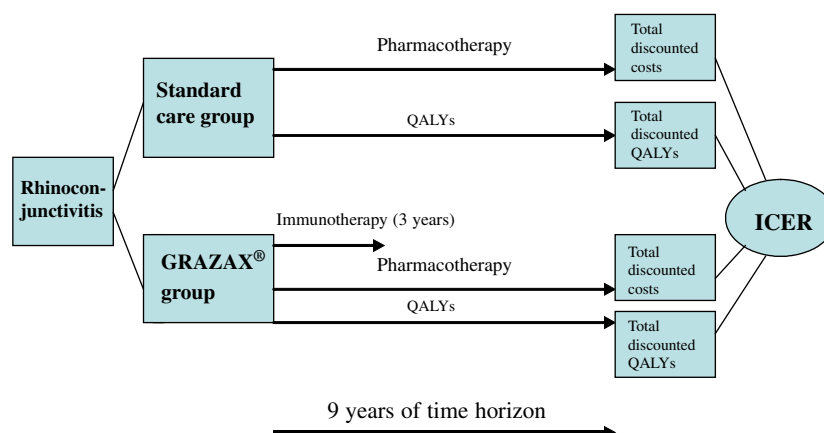


Figure 1 Outline of the pharmacoeconomic analysis.

some problems and extreme problems. In total, EQ-5D covers 245 different health states, including unconsciousness and dead. QoL was assessed by the patients on a weekly basis. To obtain QALYs the health profiles described by the patients were assigned QoL weights based on public preferences based on a random sample of approximately 3000 members of the adult population of the United Kingdom.³²

The patients who participated in the clinical trial filled in the EQ-5D questionnaire in their weekly diary (Palm Pilot) during the pollen season as well as one registration prior to — and one registration after the pollen season. We assumed constant QoL outside the pollen season and used the patients' earliest registration prior to the pollen season as a baseline measurement before the pollen season while the patients' last registration after the pollen season was used as baseline after the season. Using all the patient's EQ-5D registrations a patients' QALY value was estimated as the area under the QoL curve during the year (Fig. 2). The total number of QALYs in each of the two groups was the sum of gained QALYs for each patient. The differences between the two treatment groups were then finally calculated as the difference in the total number of QALYs between both treatment groups during a full year.

The pollen counts in Spain were extremely low during the trial. This corresponds with the fact that 2005 was the driest year in Spain since 1947, which caused the pollen season this year to be less severe in terms of pollination.^{46,47} This had an impact upon the QoL, why sensitivity analyses excluding the Spanish patients from the analysis was carried out.

Cost-effectiveness

The comparison of the two treatment strategies for grass pollen induced rhinitis was based on their relative cost-effectiveness. This was defined as the incremental cost-effectiveness ratio (ICER) of Grazax[®] versus standard care.

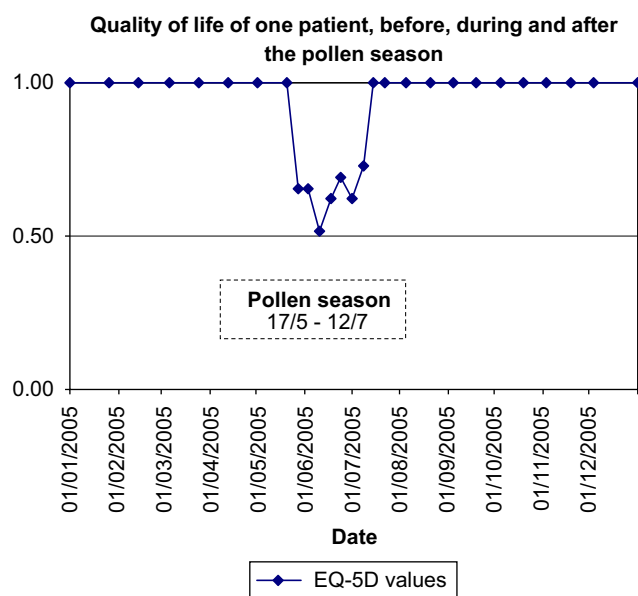


Figure 2 Example of estimation of quality-adjusted life-years (QALYs) from the clinical trial.

ICER determines the cost-effectiveness of a drug in comparison to a viable alternative.⁴⁸ It is calculated in the following way:

$$\text{ICER} = \frac{\text{Cost}_{(\text{Grazax})} - \text{Cost}_{(\text{alternative})}}{\text{Effect}_{(\text{Grazax})} - \text{Effect}_{(\text{alternative})}} = \frac{\Delta \text{Cost}}{\Delta \text{Effect}}$$

This is the difference in costs between two alternatives, divided by the difference in their effects. In this study, it is the ratio of the additional cost associated with Grazax[®] treatment over standard care divided by the gain in QALYs associated with this treatment.

For decision makers to decide which technologies to support, they need to establish a monetary value for an extra QALY. Some health care systems are beginning to state thresholds for this value.⁴⁸ In the UK, the National Institute for Health and Clinical Excellence (NICE) has stated their threshold: a drug that can generate one QALY for less than £20,000 (€29,200) compared to an alternative, is considered cost-effective, while a drug that requires more than £30,000 (€43,800) to generate one QALY is not considered cost-effective.⁴⁹ In between these limits, a drug is considered cost-effective, but additional criteria are specified to justify adoption. The relevance of these levels of cost-effectiveness is underlined by the fact that they are inversely linked to the adoption of new health technologies.^{48,50}

Results

The overall result of the trial was that Grazax[®] compared with standard care showed highly statistically significant improvements for all efficacy endpoints in terms of a 30% reduction in mean rhinoconjunctivitis symptom score and a 38% reduction in mean rhinoconjunctivitis medication score ($P < 0.0001$).²⁶

With respect to the health-related QoL in the two treatment groups compared, the EQ-5D data from the trial showed that significantly more QALYs were gained on average when treated with Grazax[®] compared with symptomatic treatment in the standard care group. The mean QALY value was 0.9626 in the Grazax[®] group and 0.9459 in the standard care group ($P = 0.017$). Hence, patients treated with Grazax[®] gained on average 0.0167 additional QALYs per season compared with patients treated with standard care. When extrapolating the QALYs gained nine years into the future, the use of grass allergen tablets compared with standard care resulted in extra 0.134 discounted QALYs during the nine-year period. This is equal to a gain of 49 days in perfect health during the period of nine years, or 5.4 days per season corresponding to around 10% extra days in perfect health during the pollen season.

When omitting the Spanish patients from the analysis, the mean QALY value in the Grazax[®] group increased to 0.9686 compared with 0.9492 in the standard care group ($P = 0.006$). Extrapolated into a nine-year perspective the discounted gain in QALYs was 0.156 equal to a gain of 57 days in perfect health.

Resource use

None of the patients in the two groups were admitted to the hospital, why this resource use parameter was excluded

from the analysis. The resource use in the two treatment groups compared is summarized in Table 3.

The number of standard visits assumed during a season in the standard care group was based on evidence from a recent European survey.⁹ In the Grazax[®] group one standard visit was assumed. With respect to additional physician visits during the pollen season for the average patient, Table 3 shows only a small and insignificant difference for the two groups compared. However, both for physician visits and for acute ward visits no difference was found between the two groups. It should be noted, however, that many patients in both groups had zero visits. Table 3 also shows that the usage of symptomatic medication was significantly higher in the standard care group compared with the Grazax[®] group, although there was no difference in asthma medication. No patients had an intake of Prednisolon in the trial.

Finally, Table 3 reveals a highly significant difference in terms of production loss in the two ways of treating rhinoconjunctivitis. The total number of hours missed from work (production loss) by the patients was 294 h (SD 5.47) in the Grazax[®] group compared with 1029 h (SD 12.81) in the standard care group. The mean number of hours missed in the Grazax[®] group was 1.06 h, while it was 3.74 h in the standard care group, indicating a production loss for the standard care group that is more than three times higher than for the Grazax[®] group.

Cost-effectiveness

The cost-effectiveness result for Grazax[®] compared with standard care for a time horizon of nine years in terms of cost per QALY gained was investigated in each of the four Southern European countries for a range of annual costs of immunotherapy with Grazax[®] from €900 to €2,900. The cost-effectiveness analyses applied country-specific unit costs and discount rates to the resource use and outcome data from the trial explained above.

The cost per QALY gained was similar in each of the four countries (Fig. 3). The highest cost per QALY gained was found in Spain, while France had the lowest costs per QALY gained. Part of this was due to differences in discount rates applied, as the discount rate in Spain is 6% as opposed to 3% in France. A higher discount rate favors the standard care group, as the cost of the higher use of symptomatic medication in the future is reduced with the discount rate. Furthermore, differences in unit costs and treatment costs were an explanation.

Using €1200 as an example for an annual cost of Grazax[®] the total costs were between €3862 and €4192 in the Grazax[®] alternative and between €1078 and €2335 in the standard care alternative. Grazax[®] accounted for between 83% and 91% of the total costs depending on country. The second highest contributor to the costs was production losses

Table 3 Resource use of the average patient in Grazax[®] and the standard care groups during the pollen season

Resource use item	Grazax [®]				Standard care			
	N	Mean	SD ^a	Share with zero visits/use (%)	N	Mean	SD ^a	Share with zero visits/use (%)
<i>Subl. immunotherapy</i>								
Grazax	–	365 tablets	–	0	–	–	–	–
<i>Visits</i>								
Physician standard visits (literature-based)	–	1 visit ^b	–	–	–	2.7–5.1 visit ^c	–	–
Extra physician visit	274	0.0766 visit	0.328	94	275	0.0909 visit	0.376	93
Acute ward visits	274	0.0146 visit	0.120	99	275	0.0145 visit	0.120	99
<i>Symptomatic medication</i>								
Loratadine ^d	316	11.9 tablets	17.61	39	318	16.6 tablets	18.71	28
Budesonide ^e	316	12.9 tablets	32.34	64	318	22.7 tablets	43.42	46
Prednisolon	316	0 tablets	–	100	318	0 tablets	–	100
<i>Asthma medication</i>								
Salbutamol	316	3.3 tablets	15.73	88	318	2.7 tablets	9.38	84
Fluticasone	316	0.98 inhal.	7.31	96	318	2.26 inhal.	12.72	93
<i>Production loss</i>								
Work hours missed ^f	278	1.06 h	5.47	87	275	3.74 h	12.81	77

^aSD = standard deviation.

^bOne standard visit assumed for the Grazax[®] group, because the intake of the first tablet in the season should be made at a visit at the GP or allergy specialist.

^cEFA.⁹ Different number of visits for each of the countries according to source.

^dLoratadine: $P = 0.0001$ (t -test, log-transformed $\log(R_i+1)$).

^eBudesonide: $P = 0.0001$ (t -test, log-transformed $\log(R_i+1)$).

^fWork hours lost: $P < 0.0001$ (t -test, log-transformed $\log(R_i+1)$).

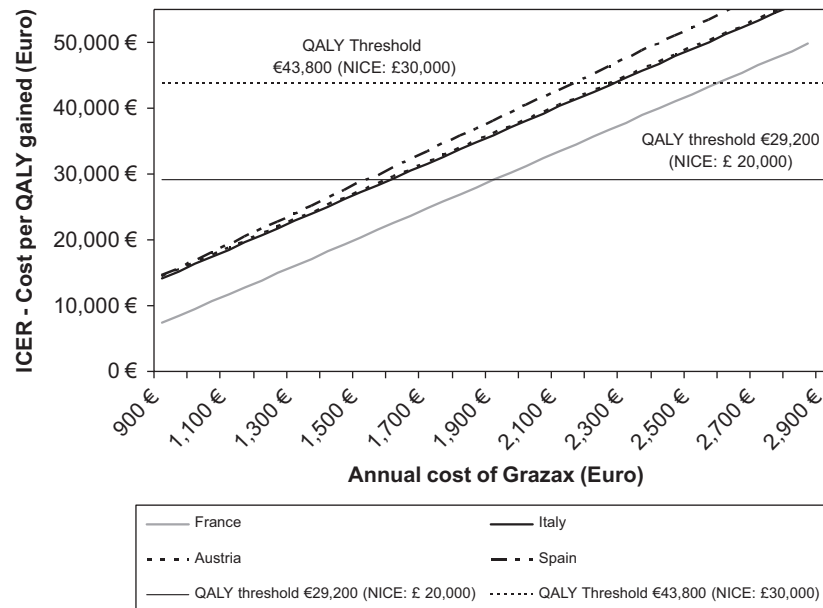


Figure 3 Incremental cost-effectiveness ratios (ICER) for Grazax[®] (cost per QALY gained).

or visits to the allergy specialist. In terms of cost-effectiveness the cost per QALY gained was €13,870 in France, €20,690 in Italy, €20,955 in Austria and €21,659 in Spain — all below the NICE cost-effectiveness threshold. Fig. 3 furthermore shows that the annual cost of Grazax[®] could be in the range from €1500 to €1900, depending on country, and still be below the official threshold value of £20,000 (€29,200) marked with the horizontal full line in Fig. 3. For the higher NICE cost-effectiveness threshold of £30,000 (€43,800) — marked with the horizontal dotted line in Fig. 3 — indicating that a technology is potentially cost-effective, the annual cost of grass allergen tablets could be in the range of €2100–€2550, depending on the country.

When including the future costs of allergic asthma, as described above, the overall cost-effectiveness result of Grazax[®] is improved even further, which was due to the contribution from the health care costs and production lost caused by allergic asthma. This is illustrated in Fig. 4, where the ICER curves have moved in the direction to the right compared with Fig. 3. In the four countries the health care costs per patient due to asthma accounted for between 4% and 26% of the total health care costs in the Grazax[®] alternative and between 54% and 242% of the total health care costs in the standard care alternative (France: 24% and 115%, Italy: 20% and 242%, Spain: 26% and 207%, Austria: 4% and 54%).

With the inclusion of future asthma costs, Spain no longer had the highest cost per QALY, but was now the country with the second lowest cost per QALY, following France with the lowest cost. Austria had the highest cost per QALY gained. Comparing with the threshold value at £20,000 (€29,200 — full horizontal line in Fig. 4) Fig. 4 illustrates that the annual cost of Grazax[®] can be in the range from €1650 to €2400 depending on the country and still be a cost-effective treatment option.

Discussion

The study found that allergen SIT with Grazax[®] from ALK-Abelló was superior to symptomatic treatment resulting in improvements for all clinical efficacy endpoints.^{23,24,26}

Prospective data collected alongside the trial^{26,31} was used in the present pharmacoeconomic analysis carried out in four Southern European countries (Spain, Italy, France, and Austria) to assess the cost-effectiveness of Grazax[®]. Patients treated with Grazax[®] used significantly less symptomatic medication against rhinoconjunctivitis and they missed significantly fewer hours from work than the patients treated with standard care alone. The QALY data collected alongside the trial also showed significant differences between the two groups in favor of Grazax[®], implying that treatment with Grazax[®] results in an improved QoL for the patients.

The present pharmacoeconomic analysis illustrates that SIT with Grazax[®] is a cost-effective intervention in the Southern European countries for a wide range of annual costs of Grazax[®] compared with symptomatic treatment (standard care). The cost-effectiveness results for each of the four countries differed only slightly with the cost per QALY being highest in Spain and lowest in France. These slightly different cost-effectiveness results were due to differences in the country-specific unit costs and discount rates applied.

An annual cost of Grazax[®] below €1500 considering a societal perspective or €1400 only focussing on direct health care costs provides cost-effectiveness for all countries even when the strictest level of the NICE cost-effectiveness threshold is applied (Fig. 5).

The cost-effectiveness result was further improved when the duration of sustained effect was prolonged past the six years of sustained effect in the present analysis. The exact duration of sustained effect is still under investigation.

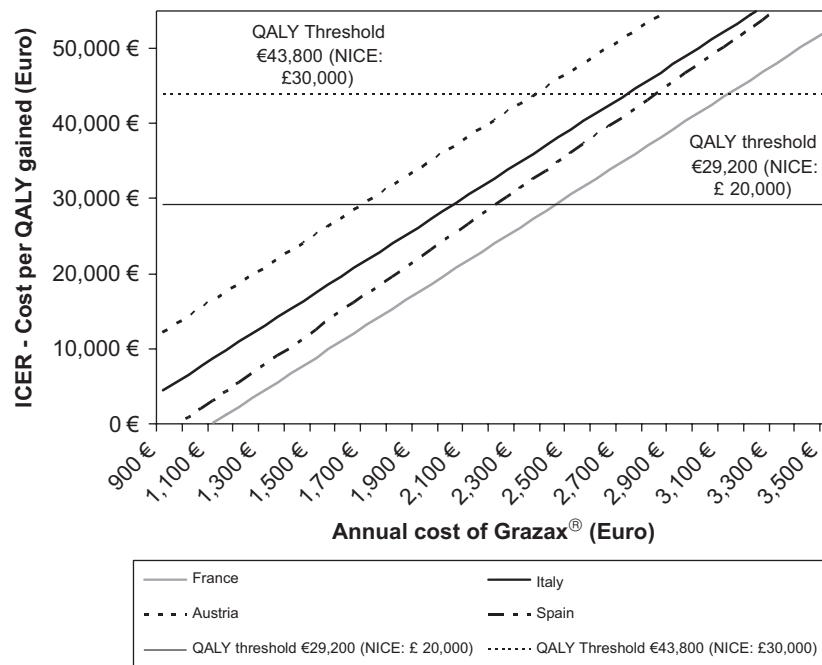


Figure 4 ICER ratios when the future costs of asthma are included (cost per QALY gained).

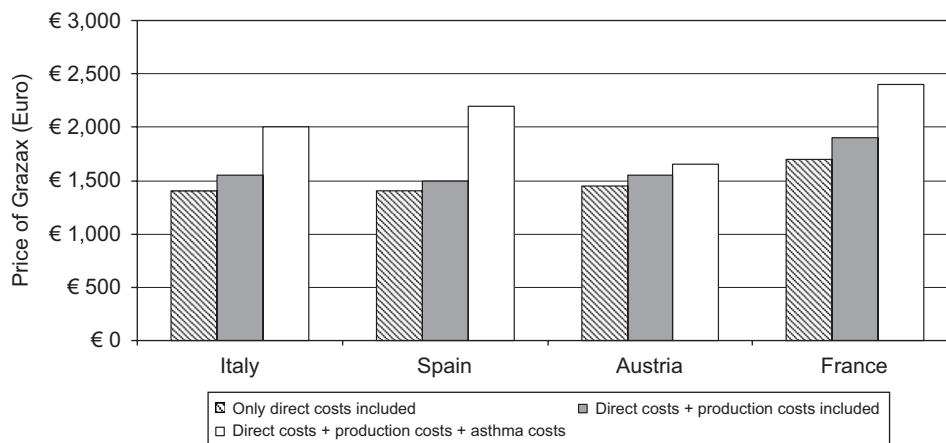


Figure 5 Annual costs of Grazax below QALY threshold of € 29,200 (NICE, ¹⁹ Euro).

In the present analysis, the placebo arm of the trial was used as a proxy for standard care. This was possible as patients in the placebo arm used symptomatic medication, which was described by the clinical trial protocol. The concomitant medication allowed was confirmed by experts in allergy from each of the four countries to be relevant and important for patients suffering from allergic rhinitis in the four countries allowing it to substitute for 'real life' standard care. If the patients had been treated with prophylactic medication this could have resulted in an increase in the use of symptomatic medication. Assuming that symptomatic medication has a positive influence on QoL this could underestimate QoL in the standard care arm of the analysis. On the other hand, the placebo effect has not been addressed. Assuming that there is an effect of placebo this could overestimate QoL in the standard care arm as this effect would not be present in 'real life' standard care.

On the basis of this analysis it can be concluded that SIT with Grazax[®] is a cost-effective treatment of grass pollen induced rhinoconjunctivitis in Southern European countries such as Spain, Italy, France, and Austria for a range of annual prices. This is supported by a previous study by Donahue et al.⁵¹ who found immunotherapy to be a less cost intensive strategy compared with standard pharmacotherapy over a ten year time horizon. SIT with Grazax[®] ought therefore to be seen as an important part of the optimal treatment for allergic rhinoconjunctivitis in Southern Europe.

Conflict of interest statement

The three co-authors have the following potential conflict of interest regarding the manuscript 'Cost-effectiveness of

Grazax[®] for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe*:

- Canonica GW Reports having received honoraria for educational presentations, and/or funding for research, and/or travel expenses, and/or for service in advisory boards from: Menarini, Alk Abello, Almirall, Altana, Astra Zeneca, Boeringher Ingelheim, Chiesi Farmaceutici, Gentili, GSK, Lofarma, MSD, Novartis, Pfizer, Schering Plough, Stallergenes, UCB Pharma, Uriach Valeas.
- Poulsen PB Have worked on this study as a consultant payed by a research grant by ALK-Abelló. MUUSMANN Research & Consulting, however, works in accordance with guidelines for pharmacoeconomic analyses.
- Vestenbæk U Is employed by ALK-Abelló, who has funded the present study and has marketed Grazax[®].

Acknowledgment

The analysis was funded by ALK-Abelló.

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