M. Bernardo[1]
J. R. Azanza[2]
C. Rubio-Terrés[3]
J. Rejas[4]

# Cost-effectiveness analysis of the prevention of relapse of schizophrenia in the ZEUS longitudinal study Ziprasidone Extended Use in Schizphrenia (ZEUS)

[1] Psychiatry Department
Hospital Clinic i Provincial
Barcelona (Spain)
[2] Pharmacology Department
Clínica Universitaria de Navarra
Pamplona (Spain)
[3] HERO Consulting
Madrid (Spain)
[4] Deparment of Research on Health ad Pharmacoeconomic Results
Medical Unit
Pfizer Spain
Alcobendas (Madrid) (Spain)

**Objective.** Estimate the cost-effectiveness of the prevention of relapse of schizophrenia in the ZEUS (Ziprasidone Extended Use in Schizophrenia Study) longitudinal study that compares ziprasidone with the option of not treating.

**Methods.** One year of treatment was analyzed using the randomized clinical trial data (ZEUS study) with a deterministic model, having cost-effectiveness analysis type, conducted from the perspective of the National Health Care System (NHCS).

**Results.** Additional mean yearly cost for worsening avoided with ziprasidone was 186 € for the mean dose, ranging from –556 € (savings) with the 80 mg/day dose and 1,014 € with 160 mg/day, which was always lower than the minimum cost of a relapse (2,830 €), considered as threshold value to establish cost-effectiveness of treatment with ziprasidone.

**Conclusions.** Prevention of relapse of schizophrenia with long-term ziprasidone is cost-effective in comparison with the option of not treating. Treatment with ziprasidone avoids relapse episodes at a reasonable cost, generating savings for the NHCS.

**Key words:**
ZEUS study. Cost-effectiveness. Ziprasidone. Schizophrenic relapse. Not treating. Prevention.

*Actas Esp Psiquiatr 2007;35(4):259-262*

## Análisis coste-efectividad de la prevención de la reagudización de la esquizofrenia en el estudio longitudinal Ziprasidone Extended Use in Schizophrenia (ZEUS)

**Objetivo.** Estimar el coste-efectividad de la prevención de la reagudización de la esquizofrenia en el estudio longitudinal Ziprasidone Extended Use in Schizophrenia Study (ZEUS) en el que se compara ziprasidona con la opción de no tratar.

**Métodos.** Se analizó 1 año de tratamiento usando los datos de un ensayo clínico aleatorizado (estudio ZEUS) con un modelo determinista, del tipo análisis coste-efectividad, realizado desde la perspectiva del Sistema Nacional de Salud (SNS).

**Resultados.** El coste medio anual adicional por reagudización evitada con ziprasidona fue de 186 € para la dosis media, oscilando entre –556 € (ahorro) con la dosis de 80 mg/día y 1.014 € con 160 mg/día, inferiores en todos los casos al coste mínimo de una reagudización (2.830 €), considerado como valor umbral para establecer el coste-efectividad del tratamiento con ziprasidona.

**Conclusiones.** La prevención de la reagudización de la esquizofrenia con ziprasidona a largo plazo es coste-efectiva en comparación con la opción de no tratar. El tratamiento con ziprasidona evita episodios de recidivas a un coste razonable generando ahorros para el SNS.

**Key words:**
Estudio ZEUS. Coste-efectividad. Ziprasidona. Recidiva esquizofrénica. No-tratar. Prevención.

## INTRODUCTION

Schizophrenia is a challenging psychiatric disorder, both on the clinical and health care level, for the patient who suffers it, for his/her family and for those responsible for his/her care[1]. It is associated to a high rate of morbidity and mortality in comparison with other chronic diseases. Its prevalence is generally found at about 1% of the adult population and it is often associated with working incapacity and social adaptation problems[2].

One of the main problems associated to treatment of the schizophrenia patient is the grade of follow-up and compliance of antipsychotic treatment since when treatment is

Study conducted with a research grant from Pfizer España.

Correspondence:
Javier Rejas Gutiérrez
Pfizer España
Av. de Europa, 20 B
28108 Alcobendas (Madrid) (Spain)
E-mail: javier.rejas@pfizer.com

abandoned, it is accompanied by relapse of symptoms and appearance of a relapse which frequently requires the patient's hospitalization in a psychiatric institutionalization unit. This entails the consequent deterioration of the disease control, negative impact on the family and financial consequences for the Society derived from hospitalization costs and psychiatric confinement[2,3]. Thus, it is deduced that schizophrenia represents one of the main components of health care costs, especially those due to institutionalization of the developed countries, including Spain[3-5].

At present, the wide experience in treatment with antipsychotic drugs has given rise to a new period in which new concepts beyond the unquestionable efficacy of these drugs are evaluated. Thus, at present, effectiveness is being evaluated with large studies on the pragmatic character such as CATIE[6]. Consequently, it is becoming increasingly important to determine efficiency (that is, cost per unit of effectiveness or cost-effectiveness) of the new treatments, in any area of medicine, and also in Psychiatry. In this sense, it seems logical to develop therapeutic recommendations aimed at optimizing the use of health care resources in this setting, and especially in schizophrenia. Relapse of this disease that requires hospitalization entails a considerable cost for society. Its avoidance would make it possible to free up financial resources for other health care sectors, resulting in greater health care efficiency levels[7,8].

Ziprasidone (ZIP) is an atypical antipsychotic that has been shown to be efficacious, effective and efficient and safe in the treatment of schizophrenia and in the prevention of relapses of these disorders[9,10]. The objective of this work was to estimate the cost-effectiveness of long term prevention (52 weeks) of relapse of treatment of the schizophrenic in comparison with the option of not treating.

## METHODS

### Pharmacoeconomic model

The study consisted in a cost-effectiveness analysis type deterministic pharmacoeconomic model. The target population was Spanish adult patients with stable chronic schizophrenia, followed-up for 12 months. The perspective of the financial evaluation was that of the NCHS. General guidelines for conducting pharmacoeconomical analyses in Spain were followed[11].

### Estimation of efficacy

The results of the ZEUS study were used in a randomized, 52-week, double blind, placebo controlled clinical trial in which efficacy of ZIP (40, 80 and 160 mg/day versus placebo) was evaluated in the prevention of relapse of schizophrenia[10]. The principal variable was relapse rate. ZIP significantly reduced the accumulated rate of relapse in comparison with placebo, with no significant differences between doses being observed. The likelihood that the relapse would require hospitalization was 0.43; 0.35; 0.36 and 0.38, at doses of 40, 80 and 160 mg daily or mean dose, respectively ($p<001$ in every case), in comparison with 0.77 with placebo.

The minimum cost described in the Psychosp study (lower limit of 95% CI) for relapse that requires hospital admission was 2,830.29 €[8], a value considered as threshold to consider treatment with ZIP as cost-effective.

### Estimation of costs

The following costs were considered: acquisition of drugs (at their dose according to the time in treatment in ZEUS study), treatment of adverse events (AE) related with the study drug and relapse that requires hospital admission. Costs per protocol, of the rescue medication in the patients with relapses that led to their dropping out of the study, pocket money, or work absenteeism were not considered. The mean number of days of treatment and the proportion of patients in each category have been estimated from the AE incidence and the survival curves of the ZEUS study. The treatment related AE cost with ZIP was estimated with the following assumptions: *a)* that the mild or moderate AEs have no associated costs; *b)* that the AEs with severe intensity cause a non-scheduled visit to psychiatry; *c)* that the serious AEs give rise to, at least, one visit to the Emergency Service, and *d)* that the abnormal laboratory values generate an additional complete laboratory analysis. The AEs observed in the ZEUS study (extrapyramidal symptoms, insomnia, etc.) will be treated with biperidene, lorazepam and propranolol at their usual doses. Finally, it was considered that the worsenings that require hospitalization would have an average cost equal to that obtained in the Psychosp study (3,421 €) that corresponds to a mean stay of 21.78 days, with a daily cost of 157 €[8].

All the unit prices included in the model are expressed in euros of the year 2005. The drug acquisition costs were obtained from the drug database of the General Counsel of the Official Association of Pharmacists and the costs of the other health care resources from the health care costs database of the Instituto Soikos.

## RESULTS

The number of patients needed to treat (NNT) to avoid the relapse episode of schizophrenia with ZIP (40, 80, 160 mg/day or mean dose) in comparison with placebo, was 2.9 (95% CI: 1.8-3.1), 2.3 (2.2-4.2), 2.4 (2.1-4.0) and 2.6 (2.0-3.7). NNT to observe relapse was 2.3; 2.9; 2.8 and 2.6 for the respective doses of ZIP and 1.3 patients for the placebo group. The approximate annual cost per patient treated with ZIP (40, 80, 160 mg/day or mean dose) was 2,724,

**Table 1** **Results of the pharmacoeconomical analysis of the prevention of relapse of schizophrenia with ziprasidone in comparison with placebo. Base case and sensitivity analysis according to daily dose of ziprasidone**

| Group | Annual costs per patient | | | | | Annual cost per relapse avoided |
|---|---|---|---|---|---|---|
| | Principal treatment | Concomitant medication | AEs | Relapse | Totals | |
| Placebo (n =75) | 0,00 € | 29.83 € | 17.84 € | 2,634.39 € | 2,682.05 € | – |
| Ziprasidone 40 mg/day (n =75) | 1,193.83 € | 33.04€ | 26.44 € | 1,471.15 € | 2,724.47 € | 124.74 € |
| Ziprasidone 80 mg/day (n =72) | 1,218.40 € | 25.64 € | 18.24 € | 1,183.76 € | 2,446.04 € | -556.63 € |
| Ziprasidone 160 mg/day (n =71) | 1,817.77 € | 32.91 € | 24.61 € | 1,224.82 € | 3,100.11 € | 1,014.70 € |
| Ziprasidone-weighted dose (n = 218) | 1,405.16 € | 30.55 € | 23.14 € | 1,296.01 € | 2,754.85 € | 186.09 € |

AEs: adverse events

2,446, 3,100, and 2,754 €, respectively, in comparison with 2,682 € per patient of placebo group. That is, incremental costs with ZIP were produced from 42, -236 (savings), 418 and 72 €, respectively. These results occurred in spite of the added cost of the acquisition of ZIP, mainly due to the fact that the yearly cost per relapses was greater in non-treated patients (2,634 €) in comparison with those treated with ZIP (between 1,183 and 1,417 €, approximately).

The mean additional yearly cost for worsening avoided with ZIP was 186 € for the mean doses, ranging from –556 € (savings) with the 80 mg/day dose and 1,014 € with 160 mg/day, approximately (table 1). These values were lower, and every case than the mean cost of a relapse (3,421 €). Consequently, they were also lower than the minimum cost of the relapse (2,830 €), considered as threshold value to establish treatment cost-effectiveness with ZIP.

## DISCUSSION

In accordance with the results of the present model, prevention of relapse of schizophrenia with ziprasidone is cost-effective in comparison with the option of not treating. The results show that ZIP produces savings, showing some incremental costs that are clearly inferior to the cost of the relapse avoided. Thus from a strictly financial point of view, it seems reasonable to consider this intervention as cost-effective. One aspect to stress, although it is not considered in the analysis, is the incidence of the hospital admissions caused by the exacerbations of the psychoses in the loss of workdays. In this regards, in comparison with the option of not treating, the yearly saving with ZIP would be 71 € per patient. This value, although modest, was calculated from the amount of minimum interprofessional salary, so that it could be underestimating the loss of real impact on work productivity. We have not found similar financial evaluations in our setting that allow us to contrast if the results found in our evaluation are consistent and close to reality of the common medical practice in our health care setting. The only comparable setting is that of Osterheider et al.[12], who also found the prevention of relapse of schizophrenia with antipsychotics cost-effectiveness.

We should take into account a series of limitations of the study. In the first place this is a model based on a non-pragmatic clinical trial. Thus its results should be considered as estimations for an average patient, that may be useful as a clinical decision-making tool. In the second place, it should be considered that no dose-dependent relationship of the efficacy of ZIP has been established. This hinders the interpretation of the results since the daily dose is an important determinant of the final cost. However, the prolonged duration of the ZEUS study (52 weeks), unusual in clinical trials in the area of schizophrenia, and the fact that both the use of resources and of unit prices of it have been obtained from Spanish studies and sources, support the consistency and applicability of the results for the clinical practice in Spain.

With the consistencies and limitations previously indicated, it can be concluded that the prevention of relapse of schizophrenia in the long term with ziprasidone is cost-effective in comparison with the option of not treating in Spain. The treatment of patients with chronic, stable schizophrenia with ziprasidone avoids a considerable number of relapse episodes, with a reasonable cost, generating savings for the National Health System.

### REFERENCES

1. Bernardo M. Redefining schizophrenia. Actas Esp Psiquiatr 2003;31:1-2.

2. Ciompi L. The effect of psychosocial factors in schizophrenia. Theoretical and practical-therapeutic consequences. Schweiz Arch Neurol Psychiatr 1995;146:207-14.
3. Almond S, Knapp M, Francois C, Toumi M, Brugha T. Relapse in schizophrenia: costs, clinical outcomes and quality of life. Br J Psychiatry 2004;184:346-51.
4. Terkelsen KG, Menikoff A. Measuring the costs of schizophrenia. Implications for the post-institutional era in the US. Pharmacoeconomics 1995;8:199-222.
5. Haro JM, Salvador-Carulla L, Cavases J. Utilization of mental health services and cost of patients with schizophrenia in three areas of Spain. Brit J Psychiatry 1998;173:334-40.
6. Álvarez E, Bernardo M, Roca M. CATIE: bienvenido al mundo real. Actas Esp Psiquiatr 2006;34:213-5.
7. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353: 1209-23.
8. Peiró S, Gómez G, Navarro M. Length of stay and antipsychotic treatment costs of patients with acute psychosis admitted to hospital. Description and associated factors. The Psychosp study. Soc Psyquiatry Psychiatr Epidemiol 2004;39:507-13.
9. Bagnall AM, Lewis RA, Leitner ML. Ziprasidona para la esquizofrenia y la enfermedad mental severa. (Cochrane Review, translated). In: La Biblioteca Cochrane Plus, 2005, number 3. Oxford: Update Software Ltd. Available in: http://www.update-software.com. (Translated from The Cochrane Library. 2005, Issue 3. Cichester, UK: John Wiley & Sons, Ltd).
10. Arato M, O'Connor R, Meltzer HY, ZEUS Study Group. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. Int Clin Psychopharmacol 2002;17:207-15.
11. Rovira J, Antoñanzas F. Economic analysis of health technologies and programmes. A Spanish proposal for methodological standardisation. Pharmacoeconomics 1995;8:245-52.
12. Osterheider M, Franken-Hiep K, Horn R. Total illness costs of schizophrenia and monetary evaluation of prevention of recurrence exemplified by a standard depot neuroleptic (flupenthixol decanoate). Psychiatr Prax 1998;25:38-43.