Title: Budget Impact Analysis of brivaracetam adjunctive therapy for partial onset epileptic seizures in Valencia Community, Spain

Short title: Budget impact Analysis of brivaracetam

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ABSTRACT

Background and Objective:

More than 30 percent of patients with epilepsy have inadequate control of seizures with drug therapy. The goal of this study is to determine the budget impact with a five year time horizon of the introduction of brivaracetam to the portfolio of approved drugs in Spain as adjunctive therapy for the treatment of partial onset epilepsy in patients over 16 years old in the Valencia Community, a Spanish region with a population of 5 million.

Methods:

The budget impact model compares the pharmaceutical expenditure on anti-epileptics in two scenarios, with and without brivaracetam. It assumes that the introduction of brivaracetam will increase proportionally to a decrease in consumption of coexisting adjunctive anti-epileptics and calculates the evolution of its consumption over five years (2016-2020). The model was designed from the perspective of the Spanish National Health System. Data on the candidate population, consumption of anti-epileptics, market share and pharmaceutical expenditure were obtained from real world data. Finally, a sensitivity analysis was carried out on the set of variables involved in the evolution of costs using a Monte Carlo simulation.

Results:

The model estimates that the target population eligible for adjunctive anti-epileptics will hold at around 2,352 between 2016-2020. Annual expenditure on anti-epileptics is approximately 3.6 million Euros. The number of patients eligible for treatment with brivaracetam would increase from 42 to 179 and annual savings of 0.09-0.37% would be created, representing 41,873 Euros in five years (0.23% of the total). The sensitivity analysis corroborates that the probability of achieving savings with brivaracetam is around 84%.

Conclusions:

Brivaracetam is a therapeutic alternative that allows savings for the health system in non-controlled epileptic patients in monotherapy, having a fixed, predictable annual cost (independent of dose) from the first day of treatment, given that the patient is within a range of therapeutic doses without the need for prior titration.

Key words

Budget impact, brivaracetam, partial-onset seizures, refractory epilepsy, adjunctive anti-epileptics

Key points

Brivaracetam is a new third generation anti-epileptic drug offering a new therapeutic alternative for concomitant therapy in the treatment of partial onset epileptic seizures, with or without secondary generalisation, in adults and adolescents above 16.

The results from this budget impact analysis suggest that brivaracetam is a cost-saving therapeutic strategy for adjunctive therapy for epilepsy in Spain

1. Introduction

Epilepsy is one of the most common chronic neurological diseases in the world, with the World Health Organisation estimating that it affects around 50 million people [1]. According a recent systematic review, prevalence of active epilepsy was 6.38 per 1,000 persons, while the lifetime prevalence was 7.60 per 1,000 persons. The annual cumulative incidence of epilepsy was 67.77 per 100,000 persons while the incidence rate was 61.44 per 100,000 person-years [2].

There are two types of epileptic seizure, generalised seizures in which all the surface of the brain is affected at the same time, and partial onset or focal seizures which begin affecting one part of the brain [3, 4]. In Spain it is estimated that around 400,000 people are affected, with nearly 60% of patients having partial onset or focal seizures [4].

Anti-epileptic treatment centres on the greatest reduction of the number of epileptic seizures, while minimising adverse effects and long-term toxicity as far as possible. Clinical evidence shows that monotherapy with anti-epileptic drugs (AEDs) is effective in 70% of patients [5]. The remaining 30% need adjunctive treatment to control the seizures [6] and, of these, approximately 25% have epilepsy that is difficult to control, refractory or resistant to AEDs. This implies difficulty in its management for the neurologist and the need to study other treatment strategies or optimise available pharmacological treatments. The importance of refractory epilepsy is in the significant decrease in quality of life with, moreover, the presence of associated morbidities (depression being the most frequent) and increased probability of early death compared to patients with controlled epilepsy [7, 8].

The annual direct cost of epilepsy in Spain is estimated to be 2,978 Euros/patient in the case of controlled epilepsy and between 4,964 [9] and 6,935 [4] Euros/patient for non-controlled, that is, between 1.7 and 2.3 times greater than with controlled patients. This proportion reaches 2.7 times greater in infantile epilepsy[3]. Furthermore, non-controlled epilepsy is associated with a greater consumption of health care resources, lower quality of life and a greater incidence of severe depression. Therefore, it places a considerable burden on the National Health Service and society, as severe levels of anxiety and depression are associated with very high costs for the health system [10].

The neurologist has more than 20 AEDs available for the treatment of epilepsy, some of which have numerous side effects and interactions that can complicate patient treatment and management, especially for those with refractory epilepsy [5]. Since 1993, more than 12 new AEDs have been approved that have an effect on seizure control and a better tolerability profile, as well as a lower risk of drug interactions. To the 4 classic or first generation AEDs (phenobarbital, phenytoin, carbamazipine and sodium valproate), 8 second generation (gabapentin, oxcarbazepine, topiramate, lamotrigine, vigabatrin, pregabalin, tiagabine and levetiracetam) and 5 third generation (retigabine, eslicarbazepine, lacosamide, perampanel and zonisamide) AEDs have been added. Nevertheless, 30% of patients are not entirely controlled [6, 11].

The choice of the most suitable AED depends principally on the patient's type of epilepsy, on the effectiveness and on the individual profile for tolerability and adverse effects. Generally, the new drugs are better tolerated, though not always more effective [12]. When comparing treatments, it is important to compare: 1) drugs with the same indication (in this case, adjunctive drugs for partial onset seizures,); 2) the need for titration and duration of this (speed in stabilising patient); 3) available pharmaceutical forms for different clinical situations; 4) dosage (which will influence in long-term compliance); 5) cost/treatment/day (affordable for the health service); 6) efficiency and effectiveness in real life; 7) safety and interactions profile (associated with being a 1st, 2nd or 3rd generation drug).

Brivaracetam is a new third generation AED offering a new therapeutic alternative for concomitant therapy in the treatment of partial onset epileptic seizures (POS), with or without secondary generalisation, in adults and adolescents above 16 years of age. This drug was approved by the European Medicines Agency in January 2016 [13]. Unlike other AEDs, it has a fixed cost, independent of dosage and has no need for titration ensuring the patient is within a therapeutic dosage range from the first day. It has a good tolerability profile and is commercialised in all the pharmaceutical forms to deal with different patient profiles (out-patients and hospitalised) [14, 15].

When introducing a new medicine to the existing portfolio for a disease, the budget impact analysis (BIA) for the new medicine is an important tool in helping to take decisions. A BIA is implemented to assess the

sustainability of the use a new technology, in this case a new drug. As such, the goal of this study was to determine the budget impact of the introduction of brivaracetam to the portfolio of approved drugs in Spain as adjunctive therapy for the treatment of POS in patients over 16 years of age with a five year time horizon in the Valencia Community (VC), a Spanish region with a population of 5 million.

2. Material and methods

2.1 Design

The BIA model was based on the latest methodological recommendations proposed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles on good practice for BIA [16]. The model estimates the incremental budget impact of adopting brivaracetam as a treatment for POS, and is structured in six basic steps for estimating budget impact: 1) estimating the target population; 2) selecting a time horizon; 3) identifying current and projected treatment mix; 4) estimating current and future drug costs; 5) estimating change in disease-related costs; and 6) estimating and presenting changes in annual budget impact.

The starting point is the current market share of other AEDs in VC, obtained from real word data from the regional electronic prescribing system. The model simulates brivaracetam entering the market and drawing a market share in pre-defined proportions from the other available therapies. Therefore, if in year 1 brivaracetam is assumed to reach 1.77 % market share, the model simulates what proportion of brivaracetam's 1.77 % is drawn from each of the other replacement therapies. This is due to the particularly difficulty of establishing a market share in indications such as POS, given how many drugs are used in combination and the difficulty in obtaining market share data for the specific patient population (Figure 1).

The assumptions and choices for the model are: 1) all patients in year 1 are assumed to be a mix of incidental and prevalent patients; 2) the model does not take into account any treatment switch due to any reason; 3) patients are assumed to be 100% compliant to each regimen they receive; 4) for all adjunctive lines it is envisaged that when brivaracetam is introduced, the market share may grow over time, therefore the treatment mixes for the mix with brivaracetam can be adjusted from year 1 to year 5; 5) the safety profile of AEDs is considered similar.

The growth rate was calculated assuming an annual population increase of 0.05%, according to data from the National Statistics Institute (INE) 2016, and a mortality of 1.9% [4] from available data in 2013.

The third generation drugs included in this comparison are those that, according to their summary of product characteristics (SmPC), have the same indications as adjunctive for POS, with or without secondary generalisation, that is: lacosamide [17], eslicarbazepine [18], perampanel [19] , retigabine [20] and zonisamide [21] (Table 1). Retigabine was withdrawn from the market in June 2017, but is nevertheless included as it was commercially available at the time of the study (January 2016).

The model was constructed using Microsoft Excel and based on the international recommendations for evaluations of this kind [16].

2.2 Estimating the target population

The target population was: patients over 16 years of age diagnosed with epilepsy and taking AEDs, both in monotherapy and as adjunctive treatment. This was extracted from the database of the Valencian Health Department (*Generalitat Valenciana*), which registers all holders of a health card for 2013. These data were anonymised and we selected the following variables per patient: age, gender, ICD-9-CM Diagnosis Codes, drug dosage by ATC code and pharmaceutical expenditure.

To avoid selecting any patient who was being treated with AEDs for diseases other than epilepsy, the following ICD-9-CM diagnoses related to epilepsy were selected: 345.90, 345.10 and 345.50 and cross-checked with the data for drug consumption corresponding to AEDs with ATC codes N03AA, N03AB, N03AD, N03AE, N03AF, N03AG and N03AX.

The patients who suffer from POS, with or without secondary generalisation, were estimated from existing epidemiological data in the literature, as were the data on incidence and prevalence [4].

2.3 Perspective and time horizon

The budget impact is determined from the perspective of the health service of the VC with a time horizon of five years, from 2016 to 2020.

2.4 Estimating AED market share and treatment mix

To obtain the market shares, the consumption data for AEDs was crossed with the diagnoses of epilepsy in order to extract drug consumption for uses other than epilepsy.

Table 2 shows the total market share of each AED for treating epilepsy. The first column shows the total market share for each AED, the second the percentage of each AED used as monotherapy, the third column shows the percentage of each AED used as adjunctive treatment and the last column gives the total annual pharmaceutical expenditure.

The total pharmaceutical expenditure on AEDs was 15,342,650 Euros, with the AEDs included in the model accounting for 32.33% of the total (4,960,118 Euros) with a share of 9.78%. The percentage of patients in monotherapy was 3.25% (447 patients) and those treated with adjunctive therapy 14.10% (2,395 patients).

The market shares are adjusted to the treatment of partial onset seizures with the AEDs introduced into the model as adjunctive therapy. The simulation of how the market share varies on the introduction of brivaracetam is shown in Table 3.

To estimate the initial market share of brivaracetam, the patients considered eligible for treatment with brivaracetam were those not controlled by the other therapies (Table 2). The model simulates the entry of brivaracetam on the market with a predefined share which is extracted from the other available therapies and proportional to their share. This approach was adopted in order to reduce the work of compiling data on the present market share of all the relevant substitute therapies. Table 3 shows the number of patients there would be for each of the five years in each therapy.

2.5 Estimate of costs

The base year for the costs considered in the model is 2016. To calculate the average daily costs for each drug, data was used from the Ministry of Health, Social Services and Equality (*Ministerio de Sanidad Servicios Sociales e Igualdad*) [22] and BOT-PLUS [23], taking the ex-factory price.

All AEDs except brivaracetam have a titration phase on initiating the treatment, varying between several days and several weeks. During this phase treatment is not effective, as the dose is gradually increased daily until it reaches the effective dose. The costs associated with this titration for each drug must be reflected in the model and were calculated from the dosage scale given in the approved SmPC for each over the time period established to reach the effective treatment dose [24]. These titration costs have been distributed over the five years of the study.

The average daily costs of the maintenance phase for each AED were calculated according to the average daily dosage, which includes all the drugs included in the model having the same indications as brivaracetam. The dose considered was that stated in the SmPC. In accordance with the ISPOR guidelines [16], costs were considered with a discount rate of 0%, for the base case. Table 4 shows the cost/treatment/day for each AED for the average dose considered and the additional cost of the initial titration phase.

The average daily cost of monotherapy treatment must also be added to the adjunctive treatment cost for each patient. This cost is calculated as an average of the most common therapies (carbamazipine, lamotrigine, oxcarbazepine, topiramate and valproate).

Dosage and frequency for the drugs is based on the SmPC of each product [13]. The pharmacological cost of the therapies studied is tied to the delivered dose. The number of days of treatment considered is 365 per year.

Costs not related to the drugs, such as medical visits, hospital admissions and emergencies have not been included in the BIA, which is limited only to the costs of the adjunctive anti-epileptic drugs.

2.6 *Sensitivity analysis*

In order to analyse the robustness of the results, a sensitivity analysis was carried out with regard to those parameters of the model considered to have greater uncertainty associated with the values used in the base case [25].

A one-way sensitivity analysis of the budget impact (BI) was performed for the cost variation of the daily dosage of brivaracetam (alternative 1), and for increasing the brivaracetam market share by 10% (alternative 2), keeping the other variables constant.

Additionally, a probabilistic sensitivity analysis (PSA) was performed. In a Monte Carlo simulation, 1,000 interactions were carried out in which multiple variables introduced into the BIA varied simultaneously. The cost of the daily dose behaved as a random variable of normal distribution with an average price of 4 Euros and a typical deviation of 5% of the average (0.2 Euros), being able to adopt any value belonging to the distribution. Effectiveness randomly varied between 50% and 100%. Market share followed the random values of normal distribution with an average from initial values and a typical deviation of 5% of the average. Discount rate varied randomly between 0% and 3%.

From the Monte Carlo simulation we obtain the average BI and standard deviation and the cumulative probability distribution to establish the probability of a negative (savings) or positive (increased cost) BI.

3. Results

3.1 *Market size*

In 2013 there were 4,714,840 people registered with a health card out of a VC population of 4,931,281. Of these, 82.58% (3,893,421) were over 16 years old. 26,972 had a diagnosis of epilepsy (50.8% men), with an average age of 51.32. Therefore, the percentage of patients with epilepsy among those over 16 years old in the in the VC for that year was 0.69%.

Given the prevalence of partial onset epilepsy is 60% [3], from the total of patients diagnosed with epilepsy the approximate number of patients with partial onset epilepsy will be 16,183, and of these a total of 15,015 will be prevalent and 1,168 incidental.

Only 22,676 (84%) of the patients diagnosed with epilepsy in the database took AEDs for treatment and, as such, this study is centred on this 84%. Of these patients, 61.9% are treated with monotherapy (14,035) and 38.1% with adjunctive treatments (8,641).

The potential population for treatment with brivaracetam are those patients using adjunctive treatments. Of the 8,641 patients being treated with adjunctive therapy, 14.10% (2,395) take one of the AEDs considered in the BIA model.

For the first year studied (2016), the model is based on a population of 2,352 patients, the result of extrapolation from the population of 2013 to 2016, according to the population growth and mortality data considered.

3.2 *Pharmaceutical expenditure*

The model presents results for the annual cost per patient, calculated from both the titration phase (only attributable to the first year) and maintenance (average dose for the following years).

Table 5 shows the evolution of the total daily costs of the medicines according to the evolution of the patients and the market share of each of the treatments. The amount according to the number of patients who follow each treatment (Table 3) is calculated for each year from the daily unit cost.

Brivaracetam titration costs are zero, as it can be initiated with an effective dosage, while the other AEDs have the additional costs shown in Table 5.

Supposing for the base case that the share of brivaracetam increases from 1.77% to 7.59% in five years (Table 3), the drug with the greatest displacement would be lacosamide, which would lose a market share of 2.32%, due to the way in which the calculations of drug displacement were made according to their initial market share.

3.3 *Budget impact*

The population of the VC suffering from POS and eligible to take brivaracetam was 2,352 patients in 2016 and is expected to stay more or less constant until 2020. Assuming the market share will increase linearly with time. Table 6 shows the total cost of medication in the reference scenario (without brivaracetam) and the new scenario (with brivaracetam).

In the reference scenario the total cost of the medication is estimated at 3.608 million Euros in the first year, increasing to 3.615 million Euros in the fifth year (up 0.20%), while in the new scenario the total cost would hardly vary in the five years (Figure 2).

In Table 6, it can be seen that the budget impact estimated as the difference between both scenarios is negative, thus representing a saving, and the absolute value is increased from 3,085 to 13,257 Euros. Over the total of the five years of the study, the introduction of brivaracetam on the market entails savings of 41,873 Euros, that is, 0.23% of the total budget. Savings from lower acquisition costs is 85.12% of the total and savings for reduced titration costs is at 14.9%.

3.5 *Sensitivity analysis*

Table 7 shows the result of a one-way sensitivity analysis. A 1% decrease of the daily dosage cost of brivaracetam implies an increase in budget savings of 19.7%, with the percentage of savings on the initial budget being 0.28% for a five-year time horizon, that is, 0.05% greater than in the base case. An increase in cost of 1% would produce the opposite effect.

A variation of 10% greater than in the base case in the introductory market share of brivaracetam would result in 10% budget savings, with the percentage in savings on the initial budget being 0.26%, that is 0.02% greater than in the base case.

In the PSA we obtained a pattern of normal distribution of BI with an average of -33,719 Euros and a standard deviation of 33,844 Euros. The probability that the BI entails a saving for the National Health Service is 84%, which corroborates the robustness of the analysis with the probability obtained in these results (Figure 3).

4. Discussion

The BIA compares the scenario with and without brivaracetam, taking into account the population eligible for treatment with brivaracetam, the market shares of other adjunctive treatments and their variation on linearly introducing brivaracetam.

The budget impact is conditioned by the displacement power of brivaracetam, which may be different to that considered and reflects an increasingly large budget saving from 0.09% in 2016 to 0.37% in 2020, an annual increasing average of 0.07%. Furthermore, the displacement of the other existing AEDs takes place in function of their initial market share, due to which the most used will also be the most displaced in the model.

The source is a real life database of AED consumption for epilepsy in the VC, with the correct figures for the adult population with health card and the prevalence of epilepsy, as well as present consumption of different drugs on the market. The prevalence obtained was 0.69% of the adult population. The percentage of patients being treated by monotherapy is 61.89%, which is different from other national data of 70%.

The results obtained for the VC can be extrapolated for the national population, in which there were 47,155 adult patients with partial onset epilepsy in 2016, to give savings of 824,431 Euros over five years. This

estimate of the target population for the whole of Spain was taken from 80% of the national population being over 16 and epidemiological data from the literature, and not from real data on disease burden.

Therefore, this BIA shows that the gradual introduction of brivaracetam in the VC creates a saving in the health service budget, with the amount depending fundamentally on the estimates used concerning the brivaracetam market share, costs and market penetration throughout a five year time horizon.

In the base case, average global savings are estimated to be 41,873 Euros in five years, which is 0.23% of the cost attributable in this period to anti-epileptic therapies in patients with partial onset seizures in adjunctive treatment.

The savings in titration become increasingly relevant in the period considered, as the titration costs of brivaracetam are equal to zero, while the therapies with the other AEDs it would replace are always positive.

In the first year of the analysis, therapy using brivaracetam can create a positive BI, though these additional costs are compensated by the savings in titration costs over the following years. Effectively, this lack of need for titration together with its fixed cost in treatment/day (independent of dosage) are two of the reasons that would justify the potential savings associated with use of brivaracetam.

The budget savings obtained could be even greater, due to the treatment-day cost of brivaracetam being established at 4.00 Euros, independently of the dose used. Therefore patients who need to increase their dose/day would cost the health system the same and it would help in controlling very refractory patients. Any increase in dose of the other co-adjunctive AEDs considered would, by contrast, bring with it an increase in the treatment/day cost. This effect helps decision-making regarding health management, as the BI would not be affected by a change of dosage of brivaracetam for a specific situation.

The majority of the limitations ascribable to the use of assumptions have been dealt with by the sensitivity analysis carried out to test the robustness of the model and to determine the impact on the final result of changes in the most sensitive variables. Nevertheless, there are other kinds of limitations in the model where uncertainty could not be reduced and these must be taken into account:

It is a future projection model of the use of a drug based on multiple assumptions and on the attitude of clinicians to the introduction of brivaracetam to the AED market. If this attitude is different to the expected, the brivaracetam market share could be different to that analysed in this study. Nevertheless, the sensitivity analysis shows that even with significant variation in the expected market share, the savings for the health service remain important.

Only the costs of the medication were included, which implies the analysis does not take into account other associated health costs, such as medical visits, etc. The results of the BIA presuppose, therefore, that these other costs are similar for any other scenario, nor does it incorporate other supposed savings regarding costs of admissions or emergencies [26]. Nevertheless, these savings would be shared between all the AEDs proportionally to their market share.

The dosages considered in the base model could be underestimating the average real dosages being used by the patients. In this case, the BIA obtained in the base case corresponds to a conservative scenario and the savings could be greater.

The assumptions that the effectiveness of brivaracetam is 100%, the discontinuation rate is 0%, compliance is 100%, and that all patients remain to the end of the treatment, imply a certain removal from clinical reality. Nevertheless, for the purpose of the BIA, this supposition is neutral, as it applies equally to all the drugs considered.

The assumption that there will be no dosage increase for any drug throughout the five years of the analysis is unrealistic in clinical practice, especially with certain drugs. This would, however, contribute to greater savings in the BIA.

We believe that these effects compensate each other and that, therefore, the figures we reach in our analysis show the real range of savings for the Spanish Health Service supposed by the introduction of brivaracetam. The analysis is sufficiently robust and shows savings for important variations of the parameters introduced in the analysis, given that the Monte Carlo simulation shows the probability for savings is 84%, even when the parameters introduced in the analysis vary.

Having therapeutic alternatives available contributes to the sustainability of the health service, as well as increasing possibilities for treatment for patients and for the health service professionals. As such, brivaracetam is a therapeutic alternative that will provide savings to the health service for non-controlled epileptic patients in monotherapy [14, 15].

5. Conclusions

The budget impact shows that the introduction of brivaracetam on the market provides savings in costs, due in part to the lowering of acquisition costs, given that the price of brivaracetam is less than other drugs with a high present market share, and also because of the decrease in titration costs in the scenario with brivaracetam.

Even with the limitations mentioned above, the analysis concludes that the use of brivaracetam in the Valencian market in patients who do not show a suitable response to conventional AEDs could produce net savings of 41,873 Euros in five years.

Based on these savings, regional and national health services should promote the choice of rational and cost-effective therapeutic strategies, fundamentally in chronic conditions such as epilepsy, which ensure long-term compliance with the treatment and favour control of the pathologies.

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Table 1. List of selected comparators according to indication

Anti-epileptic	Indication	Dosage	Nº days titration	Main action mechanism	Pharmaceutical form	Approved dosage range according to DS	Dose applied in model
Retigabine*	Drug-resistant partal onset (ADJUNTIVE)	3x/day	56	K + channel activation	Tablets	600-1200 mg daily	900 mg daily
Perampanel	Generalised and partal (ADJUNTIVE)	1x/day	33	Glutamatergic inhibition	Tablets	2-12 mg daily	8 mg daily
Eslicarbazepine	Partal onset (ADJUNTIVE)	1x/day	14	Na + channel inhibition	Tablets	400-1200 mg daily	800 mg daily
Lacosamide**	Partal onset (ADJUNTIVE)	2x/day	11	Na + channel inhibition	Tablets intravenous	200-400 mg daily	300 mg daily
Zonisamide	Partal onset (MONOTHERAPY or ADJUNTIVE) (ADJUNTIVE)	1-2x/day	14/28	Ca T thalamic channel inhibition	Capsules	200-500 mg daily	400 mg daily
Brivaracetam**	Partal onset (ADJUNTIVE)	2x/day	0	Binding to SV2A	Tablets, oral solution, intravenous	50-200 mg daily	100 mg daily

Mg: milligrams; DS: data sheet; * Withdrawn from market in June 2017

Compiled from data published in authorised summary of product characteristics. Spanish Agency of Medicines and Medical Devices (AEMPS)

** Lacosamide and brivaracetam may be used intravenously in special hospital clinical situations, such as status epilepticus or surgical operations. Dosage is variable.

Table 2. Market share of AEDs and pharmaceutical expenditure in VC: % Market share, % patients in monotherapy and % patients in add-on treatment.

AED	Market Share %	% in monotherapy	% add-on	Pharmaceutical expenditure (€)
Carbamazepine	8.3	9.3	7.6	132,667
Clonazepam	6.4	2.1	9.2	46,449
Ethosuximide	0.1	0.0	0.2	7,332
Phenobarbital	4.2	2.1	5.6	34,542
Phenytoin	5.8	5.3	6.1	49,476
Primidone	0.5	0.4	0.6	13,466
Valproic acid	16.3	20.2	13.8	641,081
Valpromide	0.1	0.1	0.1	1,816
Total classic	**41.7**	**39.5**	**43.2**	**926,829**
AED	Market Share %	% in monotherapy	% add-on	Pharmaceutical expenditure (€)
Gabapentin	3.1	3,0	3.2	132,421
Lamotrigine	10.1	11.4	9.3	1,105,525
Levetiracetam	24.3	34,0	18,0	6,639,228
Oxcarbazepine	3.5	4.1	3.1	286,374
Pregabalin	3.5	1.8	4.7	686,281
Rufinamide	0.1	0.0	0.1	83,987
Tiagabine	0.1	0.0	0.2	24,159
Topiramate	3.8	3,0	4.3	521,887
Vigabatrin	0.1	0.0	0.2	26,620
Total 2nd generation	**48.6**	**57.3**	**43.1**	**9,506,482**
AED	Market Share %	% in monotherapy	% add-on	Pharmaceutical expenditure (€)
Eslicarbazepine	2.5	1.3	3.3	1,408,626
Lacosamide	3.6	0.9	5.5	1,937,087
Perampanel	1.0	0.0	1.6	399,520
Retigabine	0.1	0.0	0.2	32,825
Zonisamide	2.3	0.9	3.2	1,131,281
Total 3rd generation	**9.5**	**3.1**	**13.8**	**4,909,339**
Total	**100**	**100**	**100**	**15,342,650**

* Valencian Health Authority, Electronic Prescription System. 2014. Prescriptions for epilepsy diagnoses only.

** Patient with two or more add-on AEDs combined.

Table 3. Initial market share and estimated variation for the following years.

AED	Market Share 3rd Generation %	Adjusted to 100% %	2016 Patients	%	2017 Patients	%	2018 Patients	%	2019 Patients	%	2020 Patients	%
Eslicarbazepine	3.28	23.91	553	23.50	544	23.1	536	22.8	528	22.41	521	22.1
Lacosamide	5.46	39.80	919	39.08	905	38.4	891	37.8	878	37.26	867	36.8
Perampanel	1.59	11.59	267	11.36%	263	11.2	259	11.0	255	10.84	252	10.7
Retigabine	0.20	1.46	34	1.45	34	1.4	33	1.4	33	1.38	32	1.4
Zonisamide	3.19	23.25	537	22.83	528	22.5	520	22.1	513	21.77	506	21.5
Brivaracetam			42	1.77	80	3.4	116	4.9	149	6.34	179	7.59
	13.72	100	2,352	100	2,353	100	2,354	100	2,355	100	2,357	100

Table 4. Cost of drugs and titration

AED (Average daily dose)	Cost/treatment/day (€)*	Titration phase cost (€)
Zonisamide (400mg/day)	3.55	51.72
Perampanel (8mg/day)	3.78	186.48
Retigabine (900mg/day)	3.80	106.56
Brivaracetam **(independent of dose)**	4.00	NA
Lacosamide (300mg/day)	4.48	31.38
Eslicarbazepine (800mg/day)	4.48	31.36
Average cost of concomitant monotherapy	0.60	

* Ex-factory price

** NA: Not applicable no titration is required

Table 5. Daily cost according to market penetration

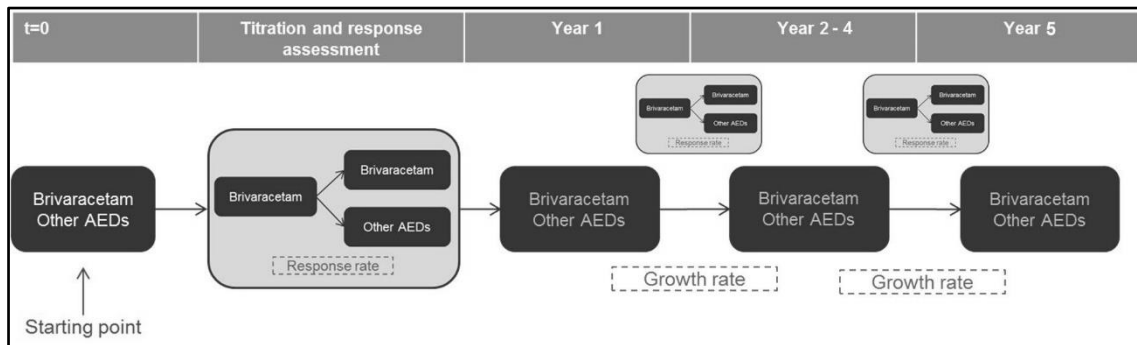| Adjunctive therapies	Daily cost/unit (€)	2016 (€)	2017 (€)	2018 (€)	2019 (€)	2020 (€)
Eslicarbazepine acetate	4.48	2,476	2,437	2,400	2,365	2,334
Lacosamide	4.48	4,118	4,052	3,990	3,932	3,882
Perampanel	3.78	1,010	994	979	965	952
Retigabine	3.8	130	128	126	124	122
Zonisamide	3.55	1,906	1,876	1,847	1,820	1,797
Adjunctive therapies	Titration costs (€)	2016 (€)	2017 (€)	2018 (€)	2019 (€)	2020 (€)
Eslicarbazepine acetate	31.36	3,467	3,412	3,360	3,311	3,268
Lacosamide	31.38	5,769	5,677	5,590	5,509	5,438
Perampanel	186.48	9,968	9,809	9,659	9,518	9,396
Retigabine	106.56	727	715	704	694	685
Zonisamide	51.72	5,554	5,465	5,382	5,303	5,235

Table 6. Summary of results

Budget forecast without brivaracetam	2016	2017	2018	2019	2020
Acquisition costs (€)	3,582,066	3,583,857	3,585,649	3,587,442	3,589,235
On initiation of AED (titration) (€)	25,943	25,956	25,969	25,982	25,995
Total w/o brivaracetam (€)	3,608,009	3,609,813	3,611,618	3,613,424	3,615,231
Budget forecast with brivaracetam	**2016**	**2017**	**2018**	**2019**	**2020**
Acquisition costs (€)	3,579,440	3,578,839	3,578,356	3,578,021	3,577,951
On initiation of AED (titration) (€)	25,484	25,079	24,694	24,335	24,022
Total with brivaracetam (€)	3,604,924	3,603,918	3,603,051	3,602,356	3,601,974
BUDGET IMPACT	**2016**	**2017**	**2018**	**2019**	**2020**
Acquisition costs (€)	-2,626	-5,017	-7,292	-9,421	-11,284
On initiation of AED (titration) (€)	-459	-877	-1,275	-1,647	-1,973
Total (€)	**-3,085**	**-5,895**	**-8,567**	**-11,068**	**-13,257**

Table 7. Brivaracetam Budget Impact, Base-case, and Alternative Analyses in Euros

BI	Base case (€)	Alternative Scenario 1 Daily cost of brivaracetam 1% lower (€)	Alternative Scenario 2 Market shares rises 10% (€)
BI without brivaracetam	18,058,095	18,058,095	18,058,095
With brivaracetam	18,016,222	18,007,974	18,012,035
Total	**41,873**	**50,121**	**46,060**

Figure 1. **Model structure of Budget Impact Analysis**

Figure 2. Budget impact estimation

TOTAL BUDGETS

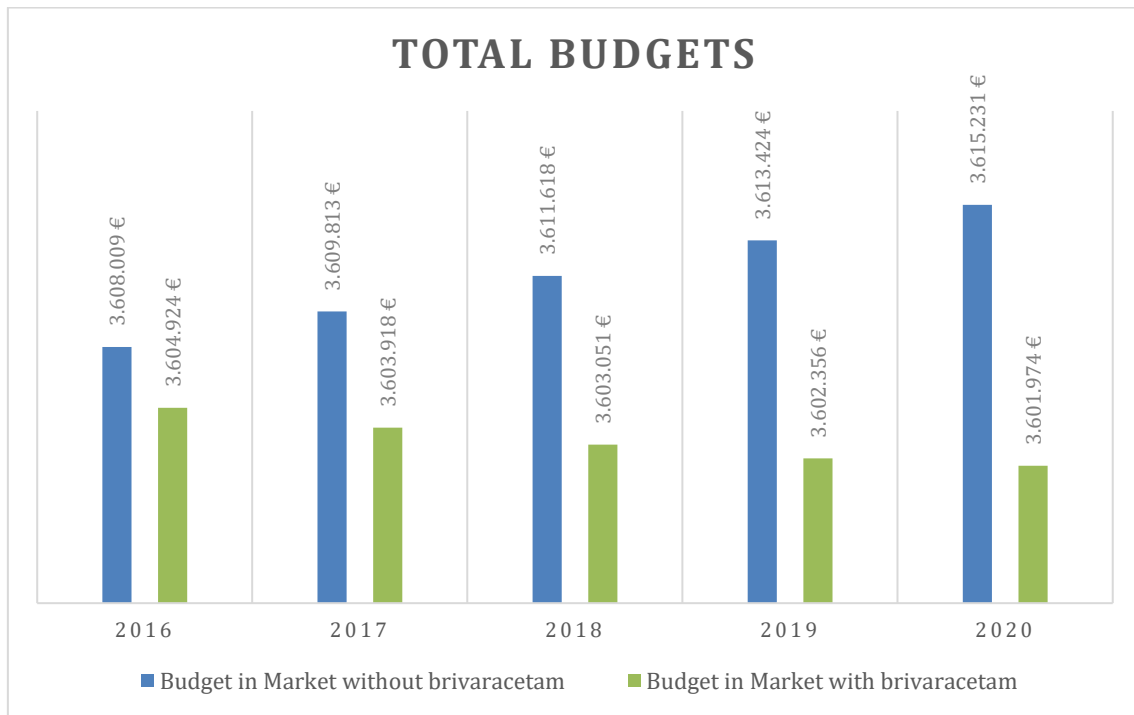|	2016	2017	2018	2019	2020
Budget in Market without brivaracetam	3.608.009 €	3.609.813 €	3.611.618 €	3.613.424 €	3.615.231 €
Budget in Market with brivaracetam	3.604.924 €	3.603.918 €	3.603.051 €	3.602.356 €	3.601.974 €

Figure 3. Cumulative probability