Special Article

Considerations for the Safe Use of Levetiracetam, Generic Type of the Antiepileptic Drug

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Antiepileptic drugs (AEDs) treatment is a treatment that most patients receive due to its effective results. In addition, most patients are comfortable with AEDs treatments. Today, there are a variety of AEDs available. Levetiracetam (LEV), which is one of new generation of AEDs (new AEDs) being widely used today, is based on the following: good pharmacological properties, good performance, a relatively low number of side-effects when compared to other AEDs, and low levels of drug interaction with other drugs or with food. It can also be used to treat epileptic patients with comorbidity diseases, as well as the elderly and pregnant women. Although LEV is well-recognized as a good medicine and has been included in the Thai national essential drug list, there are restrictions on the accessibility of this AED. This is especially true given that the price of the drug is higher than many other types of AEDs. This factor makes it impossible for most patients, who basically rely on the right to the universal health care coverage (gold card) treatment, to gain access to this type of AED. The principles for consideration surrounding the use of AEDs are as follows:

1) Indications of drug use and evidence of studies carried out on the effectiveness of the drug.

2) Patient factors, such as age, occupation, underlying diseases, regular medications, the patients' needs, and the patients' treatment rights.

3) Drug types, including pharmacological properties, histories of drug allergies, drug interactions, and drug accessibility.

4) The worthiness and effectiveness of the drug.

The Medicines and Healthcare Products Regulatory Agency (MHRA) of England has divided AEDs into the following 3 groups. AEDs are safe to change from the original to generic drugs in case that the AEDs are in Group 3 as follows: levetiracetam, lacosamide, gabapentin, pregabalin, and vigabatrin.

Keywords: Antiepileptic drug, Levetiracetam, Generic drugs

J Med Assoc Thai 2020;103(Suppl. 6): 121-9
Website: http://www.jmatonline.com

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At present, LEV includes both the original named Keppra and many other AEDs, which have generic names and a relatively lower price than the original. However, doctors, patients, and parents are worried and uncertain about the effectiveness of the generic LEV[3-5]. They are in doubt about whether or not these drugs can replace the original drug because it is commonly known that changing the AEDs from the original type to the generic type could lead to the

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How to cite this article: Tiamkao S, Tiamkao S. Considerations for the Safe Use of Levetiracetam, Generic Type of the Antiepileptic Drug. J Med Assoc Thai 2020;103(Suppl6): 121-9.

possibility of breakthrough seizures[6].

What doctors and patients need to consider when choosing original or generic AEDs is the effectiveness of the drug? It is commonly known that prior to using any generic drug, the bioequivalence (BE) of the drugs must always be studied in order to ensure that it is within the acceptable range of 80 to 120%. However, in the case of antiepileptic drugs with a narrow therapeutic index, it may be necessary to consider a narrower BE, such as 90 to 100%[7-9].

Thailand's Food and Drug Administration of the Ministry of Public Health has issued regulations requiring new generic drug manufacturers to conduct bioequivalence studies or comparative clinical studies in order that they can confirm that the manufactured drug is equivalent to the original drug so that it can be registered. In general, there are 4 ways listed below, which are used to ascertain whether the drugs have the same active ingredients, dosage, and form. Even though these drugs may be produced by different manufacturers utilizing different processes, these are the ways to determine their therapeutic equivalence and to decide whether or not they can be substituted.

1) Bioequivalence
2) Pharmacodynamic studies
3) Comparative clinical studies
4) Dissolution/release profiles

Bioequivalent studies in humans represent a widely used method because the release of the active ingredient of the drug can be measured until the ingredient is absorbed directly into the bloodstream. The Food and Drug Administration of the Ministry of Public Health announced that from January 1, 2010 onwards, the generic drug manufacturers must study bioequivalence in order to comply with the ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Study. Those drugs, which have narrow therapeutic indexes, must also have undergone bioequivalence studies. For convenience, rapidity, and cost savings, the dissolution test method can be used instead of human bioequivalence, but in only some cases[10].

Providing treatment for patients, who require medication with a narrow therapeutic index, requires careful consideration in prescribing the appropriate dosage. Moreover, it is necessary to closely evaluate and monitor both the effectiveness and the safety of drug use. To keep the drug level at the therapeutic window in the blood can be difficult due to many factors affecting the pharmacokinetics[11]. The relevant factors can be divided into 3 main parts: 1) the patient's disease conditions, 2) the treatment processes (e.g. educating the patients about diseases and medicines, observing the patient, and monitoring the medication that the patient received), and 3) the risk of using drugs with a narrow therapeutic index is related to the dose used for each patient because if each patient receives the same dose of treatment, this factor could contribute to different adverse reactions, depending on the age of each patient. Elderly patients may have changes in their pharmacokinetics, which could result in different responses to the drugs as compared to young and middle-aged patients[12].

In addition, drug-drug interactions (between food and drug or between one drug and another drug), behavior, health, and cooperation in drug use are all relevant and are difficult to constrain. Regarding the factors of the treatment process, there should be convenience and flexibility in terms of management and in the areas of patient caregivers, well-functioning systematic management, quality and consistency in laboratory follow-up checks, and in the area of the patient's educational level as well. With respect to the drug factors, such as bioavailability, bioequivalence, and the dosage formulation, they can all affect changes in the pharmacokinetics of each patient[12].

There are many generic AEDs available on the market today, such as phenytoin, carbamazepine, sodium valproate, phenobarbital, gabapentin, and lamotrigine. These AEDs have many common factors that may result in uncontrollable seizures in the epileptic patients, including low water solubility, narrow therapeutic ranges, and non-linear pharmacokinetics. With the factors mentioned, this begs an interesting question: Should changes be made in the treatment of epileptic patients from using the original drugs to generic drugs and can it be done in patients under all clinical circumstances? As many studies have revealed, the rate of switching from the generic AEDs back to taking the original drugs is up to 20 to 30 percent, which is higher than for other types of drugs. This may be due to the common symptoms of the disease and the specific properties of each AEDs, as well as the effects of repeated seizures. Therefore, consideration on whether to use the original AEDs or the generic AEDs should be carefully carried out in all of the following aspects[13-16]:

The nature of the disease

Epileptic patients respond differently to AEDs depending on the type of seizures. Moreover, depending on the prescribed dosage, the response of each patient is different, in relation to the causes of the disease, the pharmacogenetics, and the other medical conditions that must be together treated with other medications. It is possible that this could cause interactions between various drugs.

Properties of antiepileptic drugs

Most AEDs have a relatively narrow therapeutic index, while some have non-linear pharmacokinetics. In addition, those AEDs that are available in the marketplace represent a variety of types, such as immediate release, slow release, long acting, or sustained release. The dosages of the drugs used must be gradually increased in order to avoid or reduce complications and drug interactions between drugs.

Evaluation of generic antiepileptic drugs[12]

A good generic drug must have all the same properties as the original drug, including the ingredients of the drug. In addition, when taken by a patient of the same dosage, it must be able to provide the same amount of active ingredient in the body. In other words, it must be the bioequivalent (BE) to the original drug and be in accordance

with the Food and Drug Administration regulations. In addition, the proportion of area under the curve (AUC) and maximum concentration (C max) between the tested generic drug and the original drug as the reference drug must not differ more than 20 percent. With this indifferent percentage, they are considered to be the bioequivalent to each other. In contrast, generic drugs with different BE from the original drugs can have adverse effects on the patients.

In general, most of the BE studies are studies known as population BE (PBE) in which the study is conducted with a cross-randomized method of healthy volunteers. The subjects receive one generic and one original formula only one time. The results from this experiment can be used to indicate prescribability so that doctors can prescribe generic drugs and original drugs with PBE in new patients, who have never received the original drug. This can be carried out with certainty knowing that the generic drugs are likely to contribute to good treatment results. However, in the case that the patient has already received one type of original drug or generic drug and the doctor wants to change the drug to another brand of medicine, there could be a problem with the patient. The new medication might not release the same level of active ingredient that the patient has previously received. Therefore, in order to ensure that the physicians are able to switch to generic drugs instead of the original drugs (switchability) and to simultaneously sustain the same level of drug in the blood, the generic drugs must be tested for individual bioequivalence (IBE). In IBE studies, each volunteer must receive at least twice the number of original and generic drugs to determine whether the pharmacokinetic values of the original and generic drugs used in the same subjects differ or vary when each dose is given. In addition, it must also investigate whether or not the drug level is within the therapeutic window like the original drug.

In the case of the sustained release of generic drugs, BE must be conducted under steady state and fed conditions in order to evaluate and determine if the fluctuations of the drug levels and the ability to release the active ingredient are equal to the original drug, especially under conditions in which the drug is taken together with food.

Another important point is that BE studies have only been conducted on generic drugs, but there have been no therapeutic equivalence studies of the drugs. According to the physicians' experiences and the findings from many studies, 10-35% of the patients are said to have experienced seizures after changing from the original drugs to generic drugs.

Another problem is that the generic drugs come in different pill shapes and have different colors than the original drugs. Also, the names of the drugs (brands) can vary depending on the company. When taking the medications, this may result in some patients becoming confused. In addition, for some companies, the production and distribution of their generic drugs may be intermittent, which can result in problems when needing to frequently acquire replacement drugs. This may contribute to having difficulty to follow-up when there is a drug use problem. According to studies[3] by Andermann F, et al, the rate of change from generic drugs back to original drugs for patients, who had previously received the original drugs showed the following: 1) the patients receiving sodium valproate had the rate of 20.9% change, 2) clobazam (20.6%), 3) lamotrigine (12.9%), 4) statin (1.5%), and 5) SSRI (only 2.9%).

The Medicines and Healthcare Products Regulatory Agency (MHRA) of England[17] has divided antiepileptic drugs into the following 3 groups were showed in Table 1.

The above table (Table 1) shows that those AEDs are safe to change from the original to generic drugs in case that the antiepileptic drugs are in Group 3 as follows: levetiracetam, lacosamide, gabapentin, pregabalin, and vigabatrin (available in Thailand), as well as tiagabine and ethosuximide (not available in Thailand). Therefore, because repeated seizures can have effects on other diseases, the process of changing the type of AEDs should follow the above recommendations along with taking other considerations into account.

Impacts from epilepsy[12]

It is commonly known that the treatment of epilepsy requires the control of seizures for at least 2 years. Therefore, if patients have repeated seizures, they must start counting every time the symptom appears. In addition, when the seizures take place, they can lead to many consequences, such as accidents from seizures; traffic accidents, which cause

Table 1. Category 1 to 3 of antiepileptic drugs

	Advice for doctors	Antiepileptic drugs in category
Category 1	Doctor are advised to ensure that their patient is maintained on a specific manufacturer's product	Phenytoin, carbamazepine, phenobarbital, primidone
Category 2	Doctors are advised to use their judgement (in consultation with their patient and/or their carer) to determine whether it would be advisable for them to be maintained on a specific manufacture's product.	Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate
Category 3	Doctors are advised that is usually unnecessary to ensure that their patients are maintained on a specific manufacture's product.	Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin

the patients to stop operating the vehicle; a lack of self-confidence due to repeated seizures; and the cost of treatment when having to be admitted to the hospital. According to a study, which examined the money being spent by the epileptic patients in Canada for the original and the generic antiepileptic drugs, it was found that generic drug users had incurred the higher cost of $7,902 Canadian, while the original drug users had just spent $6,149 Canadian. Similarly, studies in the United States also found that when AEDs were changed from the original to the generic, more patients had been treated in emergency departments, had used ambulance services, and had been admitted to hospitals[12].

In addition, there are psychological effects that are difficult to assess because they do not only affect the patient, but the patients' families are affected as well. Parents suffer from needing to watch their babies all of the time and even miss their sleep. Parents must keep watch because seizures can arise while the babies sleep. Doctors are also affected by repeated seizures since parents can lack confidence and trust in the doctor, which can result in prosecution if the patient's parents are not satisfied due to the repeated seizures.

Therefore, it can be seen that the impact is more severe than expected. It is, therefore, not surprising that Haskins LS, et al found in their study that 80 percent of the 974 epilepsy patients surveyed did not want to change the drug from the original to the generic[13]. Likewise, 89 percent of the 435 doctors wanted the pharmacists to inform the patients, but due to fear of the above effects, it is necessary that the doctors give their consent in order to change the drug. In the case of patients with neuropathic pain, even if the effects are not equal to epilepsy, the pain affects the quality of their lives as much as the seizures do in epileptic patients.

National policies[12]

In America and in countries in Europe, clear guidelines have been established, which state that patients and doctors must be notified. Furthermore, before changing a patient's medication, they must agree because the safety of the patients is of primary concern. In Thailand, there are no such clear policies, which have been created for the country.

Patients' rights[12]

All patients should be eligible to receive the most appropriate treatment. Consideration should not be based on the cheapest treatment. In fact, no studies have shown that generic drugs are worth more than the original drugs. In addition, the patients should not be divided into groups for different drugs by considering treatment rights. Operating in this manner is tantamount to dividing patients according to a "caste system", which is not in alignment with the principles of medical treatment that are being taught in medical schools.

The worthiness of using original and generic drugs

Considering the worthiness of treatment is another issue that needs to be examined. For treatment of any disease, the worthiness or effectiveness of the treatment is always one of the main aspects to be considered because the main reason doctors choose generic medicine is to reduce the cost of treatment, which contributes to worthwhile standards of treatment.

Assessing the worthiness of treatment must be conducted carefully at all points of the costs, including medication, travel, expenses for meeting the doctor, treatment, the wastage of time, hospitalization, examination fees in the emergency room, and loss of opportunity including disability or even death. To sum up, it can be seen that to consider the worthiness of the treatment options not only implies taking the cost of drugs used for treatment into consideration, but it also requires examining many other impacts[12].

Somsak Tiamkao, et al studied a comparative study on the impacts of the costs of the immediate-release type of Phenytoin versus the extended release type of Phenytoin for medical treatment and also, assessed the worthiness of all of its epileptic effects. According to the results, it was found that the extended-release Phenytoin had been worth more than the immediate-release Phenytoin[18].

Moreover, patients with status epilepticus or acute repetitive convulsive seizure were treated with Levetiracetam (the intravenous injectable type) so that the effectiveness of the original drugs could be compared to the generic drugs, which were named "Focale". It was found that both AEDs had been effective and had had corresponding side-effects. In short, Levetiracetam antiepileptic drug of the Focale brand can be injected intravenously instead of original Levetiracetam. This can result in significantly reducing costs and in increasing the accessibility of patients, who need to use intravenously injectable Levetiracetam[2].

This AED, Levetiracetam, has been studied by researchers in many countries, including a study by Bosak M, et al of Poland in 2017. In this study, it was found that due to the high cost of the medication, 151 out of 159 epilepsy patients had changed from using the original drugs to generic drugs. It was found that 9 patients (6%) had experienced more seizures than before and that 2 patients had had to return to taking the original medication, while 6 patients (4%) had experienced side-effects, such as dizziness and drowsiness[19].

The details of patients continuing to use original drugs and those changing to generic drugs showed in Table 2 A study in Sweden by Olsson P, et al was carried out in 2019 to determine the epilepsy patients' quality of life using the epileptic assessment, QOLIE-31. The patients had originally taken Levetiracetam and then their medication was changed to the generic drugs. In the present study, a total of 32 patients were divided into 2 groups of 16[20]. The medication of the first group was changed to the generic drugs, while the second group continued to take the original drug. The results indicated that that both groups had shown no difference in the quality of life in all aspects, including anxiety due to seizures.

Furthermore, in a 2018 Italian study[21] conducted by Trimboli M, et al, 180 patients, who were using the original LEV, were the participants. In the first group, 125 patients had their medication changed to generic drugs, in

Table 2. Characteristic of patients who switched to generic LEV and continued treatment with the brand-name LEV

Variable	Patients who switched to generic LEV (n = 151)	Patients who continued treatment with the brand-name LEV (n = 8)
Age (year); median (IQR)	34 (28 to 42)	30.5 (20.5 to 44.5)
Age at onset of epilepsy (year); median (IQR)	14 (6 to 20)	8.5 (3 to 15.5)
Sex (women)	88 (58.3%)	3/8
Type of epilepsy		
Generalized	19 (12.6%)	0
Focal	125 (82.8%)	6/8
Unknow	7 (4.6%)	2/8
Duration of treatment with LEV year; median (IQR)	3 (2 to 4)	5 (4 to 5)*
Daily dose of LEV (mg); median (IQR)	2,000 (1,000 to 3,000)	2,500 (1,250 to 3,000)
Increased frequency of seizures	9 (6.0%)	0
Adverse reactions	6 (4.0%)	0
Number of AEDs used		
1	15 (9.9%)	0
2	85 (56.3%)	5/8
3	49 (32.5%)	2/8
NA	2 (1.3%)	1/8

* $p<0.01$ for the difference in duration of treatment with LEV; other differences were not significant.
AED = Antiepileptic drug, IQR = Interquartile range, LEV = levetiracetam, NA = not available

which 59 (47%) used monotherapy and 66 (53%) used polytherapy. In addition, 55 patients in the second group continued to use the original LEV without having any medication changes. The findings indicated that the patients in both groups had not shown any difference in treatment results with respect to both the number of seizures and the side-effects of AEDs. The treatment outcomes are detailed in Table 3 and Table 4, which shows the patients, who were only taking the original Levetiracetam as compared to taking generic drugs over an average duration of 24 to 48 months. For both groups, the results of the treatment did not differ. When the side effects of Levetiracetam antiepileptic drugs of both the original and the generic were solely considered, no differences were found.

A Korean study[22] conducted by Lee GH, et al in 2018 showed that 109 out of 148 patients (73.6%) had had no seizures prior to switching to generic drugs, and of those, 105 patients had had no seizures after changing the drug. Of the 148 patients, there were 7, who had had increases in seizures (4.8%), while 10 out of 148 (6.8%) had experienced reduced seizures. As seen in Figure 1, when the medication of both groups of patients (those who had been 'seizure-free' and those who had not been 'seizure-free') had been changed from the original type of LEV to the generic type, it was found that patients, who had not been 'seizure-free', had become more 'seizure-free'. Moreover, when the patients had been monitored for a long time, it was also found that the 'seizure-free' patients had increased in number from 109 to 113, while the patients, who had not been 'seizure-free', had been reduced from 39 to 35 people.

In 2016, another important study[8] by Contin M, et al was carried out in Italy. This study measured the antiepileptic drug levels in the same 362 patients when taking the original drugs and the generic drugs. The study's findings revealed that when taking both types of LEV, there had been no difference in the drug levels.

Findings from a study conducted in Italy[23] by Fanella M, et al in 2017, showed that after 36 out of 37 patients had changed from the original drugs to generic drugs, 3 of 36 patients had experienced side-effects, while the remaining 33 patients had experienced no side-effects. Furthermore, when the LEV levels had been tracked, no differences were found. Finally, the rate of those returning to use the original drugs was at 8%.

Study in 2011 by Fitzgerald CF, et al found that 4 patients had experienced increased seizures after the drug had been changed from the original to the generic and that these patients had needed to change back to the original drugs[24]. In addition, Chaluvadi S, et al published an article in the Epilepsia Journal in 2011, in which it was stated that the country's policy was to change all original drugs to generic drugs and that this had begun in 2008. It was found that among the 760 epilepsy patients in the study, the rate of switching back to take the original drugs was as high as 42.9% after changing to generic drugs[5]. The factor, which affected the drug reversion, had been the combined usage of various antiepileptic drugs. Table 5 shows the results of all 8 studies mentioned above.

In Thailand, there are many generic LEV sold. This article presents the details of the generic LEV, which is named Letta 500. The Letta was manufactured by M/s. SMS Pharmaceuticals, Ltd. of India with good manufacturing standards and in accordance with the Good Manufacturing Practices as recommended by the World Health Organization,

Table 3. Characteristic and electroencephalographic of patients who treated with original and generic Levetiracetam

	All patients (125 patients)		LEV as monotherapy (59 patients)		LEV in polytherapy (66 patients)	
	T0	T1	T0	T1	T0	T1
Seizures/month (n) (mean)	2.4	2.3	0.7	0.7	3.9	3.8
Confidence interval	0.1 to 6.4	0.2 to 6.4	0.2 to 6.2	0.1 to 6.2	0.3 to 6.6	0.2 to 6.5
(*p*-value T0-T1)	(0.71)	(0.31)	(0.65)			
Seizure/month (n)	0 (0 to 90)	0 (0 to 90)	0 (0 to 16)	0 [0 to 16]	1 (0 to 90)	1 (0 to 90)
Seizures-free patients	80 (64%)	80 (64%)	51 (86%)	51 (86%)	29 (43%)	29 (43%)
Adverse effects	31 (25)	30 (24)	15 (25)	14 (24)	16 (24)	16 (24)
(*p*-value T0-T1)	(0.86)	(0.78)				
Interictal EEG findings						
Normal	12 (10)	12 (10)	5 (8)	5 (8)	7 (10)	7 (10)
Unilateral left	26 (20)	26 (20)	9 (15)	10 (17)	17 (25)	16 (24)
(*p*-value T0-T1)			(0.91)		(0.87)	
Unilateral right	22 (18)	22 (18)	11 (18)	9 (15)	11 (16)	13 (19)
(*p*-value T0-T1)			(0.76)		(0.69)	
Bilateral	65 (52)	65 (52)	34 (57)	35 (59)	31 (49)	30 (45)
(*p*-value T0-T1)			(0.72)		(0.81)	

Data are given as median [range] or n (%).
LEV = levetiracetam

Table 4. Characteristic of patient who treated with original and generic Levetiracetam

	Keppra® monotherapy (40 patients)	Matever® monotherapy (59 patients)
Sex (M/F)	16/24	25/34
Age (years)	42.1±16.1	40.2±18.1
Age at onset (years)	21.2±17.9	22.2±17.9
Duration (years)	17.8±19.1	17.8±19.1
Family history of FC/epilepsy (n)	19	28
Seizure type (F/G)	25/15	37/22
LEV dosage (mg)	1,523.7±603.6	1,576.3±798.5
Seizure/month (n)	0.7±7.9	0.7±8.8
Adverse effect LEV related	11 (27)	14 (24)
Follow-up (months)	24.2±13.5	25.1±12.9

F = focal, FC = febrile convulsion, G = generalized, LEV = levetiracetam
Data are given as mean ± SD or n (%).

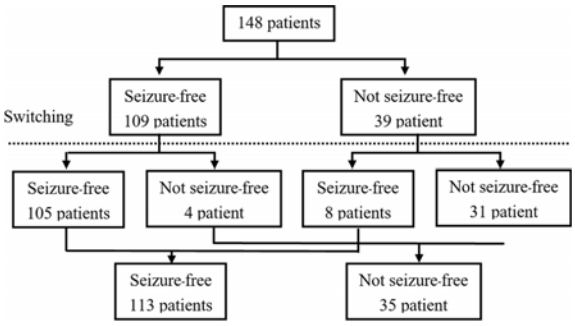

Figure 1. Number of patients who changed from original to generic Levetiracetam.

as well as in accordance with the United States Pharmacopoeia Specifications.

Levetiracetam has been classified in accordance with the Biopharmaceutics Classification System (BCS) to be in Group 1 (BCS Class I), indicating that the drug is highly soluble and highly permeable with a permeability value (Peff)) of 0.86 cm/h and with 100% oral bioavailability. The solubility of Levetiracetam in Letta was studied at a dose of 1,000 milligrams in the pH range 1.0 to 7.0. It was found that Levetiracetam had exhibited a high degree of solubility as shown in Figure 2.

In addition, regarding Letta 500's dissolution profile when compared with Keppra 500 at pH values of 1.2, 4.5, and 6.8 and with water to show the drug release according to gastrointestinal conditions, it was found that Letta 500 had released the drug in a rapidly dissolving manner. Specifically, more than 85% of the drug was found to have been released within 15 minutes under all test conditions (pH 1.2, 4.5, and 6.8 and water), as well as with the same release form as the original Keppra 500, as shown in Figure 3 to 6.

In addition, Letta 500 was found to be in accordance with the Waiver of In-vivo Bioavailability and Bioequivalence studies for immediate-release solid oral dosage forms based on a US Biopharmaceutics Classification System (USCDER). Moreover, it was approved by the Food and Drug Administration on October 20, 2017.

With reference to the bioequivalence study of the comparison between Letta 500 and the original Keppra 500, it was necessary to confirm the effectiveness of Letta 500 so that it could conform to the ASEAN criteria and to the ICH Guidelines. The findings showed that Letta 500 products had been bioequivalent to Keppra as shown in Table 6.

Conclusion

According to the information stated above, the results showed that the replacement of antiepileptic drugs (Levetiracetam) from the original type to the generic type could be carried out in accordance with the instructions from the MHRA in England. It was found to be the safest when compared to the standard antiepileptic drugs (Phenytoin, Carbamazepine, Valproate, and Phenobarbital), all of which are classified as Group 1. In other words, the type or brand of drugs should never be changed. However, with respect to the safety of the patients, it is important to closely monitor seizures and side-effects. In practice, there had been a number of cases in which the drug being administered had been changed from the original drug to the generic. Furthermore, due to repeated seizures, increased numbers of seizures, or the side-effects of using the generic drugs, it was found that the patients had had to return to taking the original drug. Consequently, this suggests that patients and their relatives should closely observe the patients' initial symptoms after the drug has been changed. This is especially true for patients, who need to use a polytherapy of AEDs and who are still are not able to control their seizures well.

What is already known in this topic?

Antiepileptic drugs (AEDs) treatment is a treatment that most patients receive due to its effective results. In addition, most patients are comfortable with AEDs treatments.

Table 5. Details of 8 studies in which the patients were switched from original to generic Levetiracetam

Studies	Bosak M	Olsson P	Trimboli M	Lee GH	Contin M	Fanella M	Fitzgerald CF	Chaluvadi S
Number of epileptic patients	159	32	125	148	147	36	4	760
Single antiepileptic drug	9.9%	15 patients	47%	45.3%	-	-	-	-
More than one antiepileptic drug	90.1%	17 patients	53%	54.7%	-	-	-	-
Rate of switching back	6%	No	No	4.8% increase in seizures	-	8%	4 patients	42.9%
Side-effects	4%	No	No difference	No difference	-	3 patients	-	-
Quality of life	-	No difference	-	-	-	-	-	-
Antiepileptic drug level	-	-	-	-	No difference	No difference	-	-

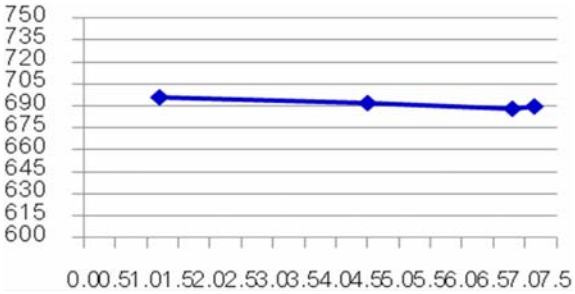

Figure 2. Graphical presentation of the pH-solubility profile.

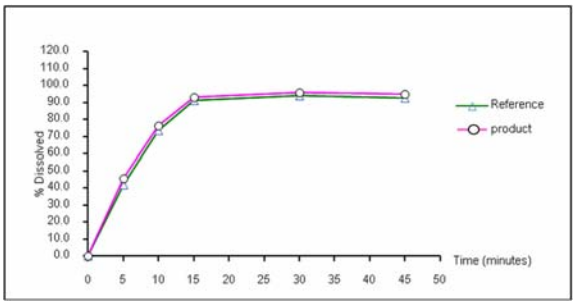

Figure 3. In vitro dissolution profiles between Keppra 500 mg (reference product) and Letta 500 (test product) in 0.1 N HCl buffer (pH 1.2).

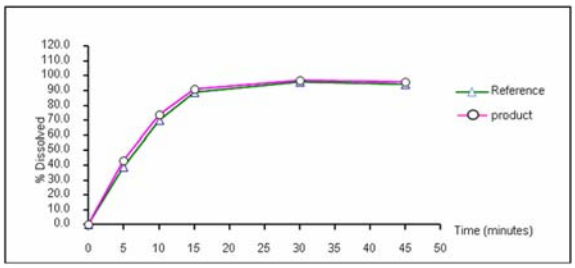

Figure 4. In vitro dissolution profiles between Keppra 500 mg (reference product) and Letta 500 (test product) in acetate buffer (pH 4.5).

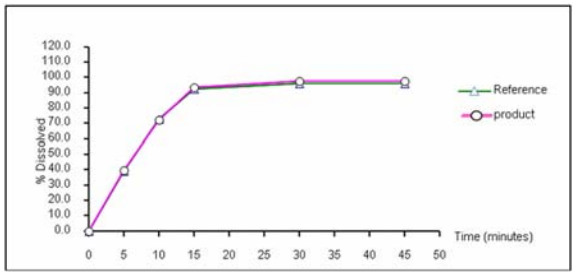

Figure 5. In vitro dissolution profiles between Keppra 500 mg (reference product) and Letta 500 (test product) in phosphate buffer (pH 6.8).

What this study adds?

Levetiracetam (LEV), which is one of new generation of AEDs (new AEDs) being widely used today, is based on the following: good pharmacological properties, good performance, a relatively low number of side-effects when compared to other AEDs, and low levels of drug interaction with other drugs or with food.

Potential conflicts of interest

The authors declare no conflicts of interest.

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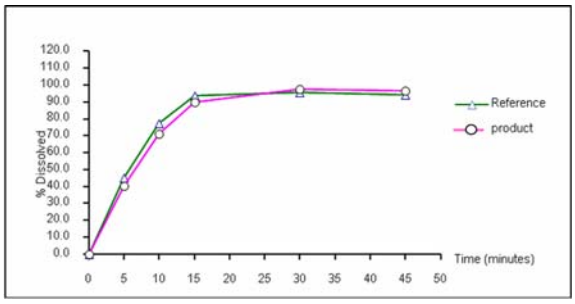

Figure 6. In vitro dissolution profiles between Keppra 500 mg (reference product) and Letta 500 (test product) in water.

Table 6. The bioequivalence of Letta is equal to that of Keppra

Parameters	Ratio of least square mean (%)	90% CI
ln C_{max}	98.56	92.41 to 105.12
ln $AUC_{0\text{-tlast}}$	99.06	96.53 to 101.65
ln $AUC_{0\text{-}\alpha}$	98.97	96.36 to 101.66

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ข้อควรพิจารณาการใช้ยากันชักลีวีไทราซีแทมชนิดชื่อสามัญอย่างปลอดภัย

สมศักดิ์ เทียมเก่า, ศิริพร เทียมเก่า

การรักษาโรคลมชักด้วยยากันชักเป็นวิธีที่ผู้ป่วยส่วนใหญ่ได้รับเนื่องจากเป็นวิธีการรักษาที่ได้ผลดี และผู้ป่วยส่วนใหญ่ก็สะดวกต่อการรักษาด้วยยากันชัก ยากันชักในปัจจุบันนั้นมีเป็นจำนวนหลากหลายชนิด ซึ่งยากันชักชื่อลีวีไทราซีแทมนั้นเป็นยากันชักรุ่นใหม่ที่นิยมใช้กันมากในปัจจุบัน เนื่องจากมีคุณสมบัติทางเภสัชวิทยาที่ดี มีประสิทธิภาพดี ผลข้างเคียงที่พบค่อนข้างต่ำเมื่อเทียบกับยากันชักชนิดอื่นๆ และมีอันตรกิริยากับยาหรืออาหารน้อยมาก สามารถใช้รักษาผู้ป่วยโรคลมชักที่มีโรคร่วมได้ รวมทั้งผู้สูงอายุและหญิงตั้งครรภ์

ถึงแม้ว่ายากันชักชื่อลีวีไทราซีแทมนี้จะเป็นยาที่ดี มีประสิทธิภาพและอยู่ในบัญชียาหลักแห่งชาติก็ตาม แต่ก็มีข้อจำกัดในการเข้าถึงยากันชักชนิดนี้ เพราะราคายาที่ผู้ป่วยส่วนใหญ่ต้องใช้นั้นมีมูลค่าสูงกว่ายากันชักชนิดอื่น ทำให้การเข้าถึงของผู้ป่วยส่วนใหญ่ที่สิทธิการรักษาบัตรทองนั้นไม่สามารถเข้าถึงการรักษาด้วยยากันชักชนิดนี้ได้

หลักการพิจารณาเลือกใช้ยากันชักชนิดใดนั้น มีหลักการพิจารณาจากองค์ประกอบ ดังนี้

1) ข้อบ่งชี้ของการใช้ยา และหลักฐานการศึกษาประสิทธิภาพของยานั้นว่าได้ประโยชน์หรือไม่

2) ปัจจัยด้านผู้ป่วย ได้แก่ อายุ อาชีพ โรคประจำตัว ยาที่ใช้ประจำ ความต้องการของผู้ป่วย และสิทธิการรักษา

3) ชนิดของยาได้แก่ คุณสมบัติทางเภสัชวิทยา ประวัติการแพ้ยา อันตรกิริยา และการเข้าถึงยาของผู้ป่วย

4) ความคุ้มค่า และประสิทธิภาพของยานั้น

Medicines and Healthcare Products Regulatory Agency: MHRA ประเทศอังกฤษ แบ่งกลุ่มยากันชักเป็น 3 กลุ่ม ยากันชักนั้นมีความปลอดภัยในการเปลี่ยนจากยาต้นแบบเป็นยาชื่อสามัญ กรณียากันชักนั้นอยู่ในกลุ่มที่ 3 ได้แก่ ลีวีไทราซีแทม, ลาโคซามัย, กาบาแพนติน, พรีกาบาลิน, ไวกาบาติน