A new generation of antiepileptic drugs (AEDs) is characterized by complex and multiple mechanisms of action which influence signal transmission in the central nervous system. This extended pharmacological profile has highlighted opportunities to identify new possibilities for these drugs outside epilepsy. Recently studies have focused on their possible use in addiction therapy.

Zonisamide, a benzisoxazole derivative, is one of the new generation of AEDs that has a broad combination of complementary mechanisms of action, which may offer a clinical advantage over other antiepileptic agents. By altering the fast inactivation threshold of voltage-dependent sodium channels, zonisamide reduces the sustained high-frequency repetitive firing of action potentials (Biton, 2007; Brodie et al., 2012). Zonisamide also inhibits low-threshold T-type calcium channels in neurons, which may prevent the spread of seizure discharge across cells (Perez-Reyes, 2003; Miwa and Kondo, 2011). In addition, zonisamide is a weak inhibitor of carbonic anhydrase (Thöne et al., 2008). However, this mechanism is not believed to contribute to the antiepileptic activity of zonisamide (Brodie et al., 2012). Although zonisamide also seems to alter the metabolism of dopamine, serotonin and acetylcholine, it is not clear to what extent these effects on neurotransmitters are involved in the clinical actions of the drug (Biton, 2007; Brodie et al., 2012). In addition to these actions, recent evidences suggest that zonisamide may exert neuroprotective actions, independent of its antiepileptic activity (Rösler et al., 2010). A wide spectrum of pharmacological activity of zonisamide has prompted research aimed at finding other, besides treatment of epilepsy, therapeutic indications for the drug’s use (Faught et al., 2001; Sackellares et al., 2004; Brodie et al., 2005; Lu et al., 2011). Zonisamide has been suggested to have beneficial efficacy in various neurological and psychiatric diseases. Migraine (Drake et al., 2004; Bermejo and Dorado, 2009; Mohammadianinejad et al., 2011), neuropathic pain (Alti and Dogra, 2005), essential tremor (Handforth et al., 2009), impulse control disorders (Bermejo et al., 2010), drug-resistant bipolar disorder (Anand et al., 2005; McElroy et al., 2005) and Parkinson’s disease are possible uses of this drug (Murata et al., 2007; Bermejo and Anciones, 2009; Murata, 2010). Furthermore, experiments using an animal model of ischemia revealed neuroprotective properties of the drug (Hayakawa et al., 1994; Minato et al., 1997; Noda et al., 1999; Costa et al., 2011).

In the limited access animal model of drinking zonisamide decreased ethanol consumption in rats and alcohol-prefering mice (Knapp et al., 2007). The results of initial clinical trials are positive, but due to their limited range, they need to be broadened. In fact, zonisamide reduced ethanol consumption in 12-week clinical trials in addicts (Arias et al., 2010; Rubio et al., 2010a). It has been suggested that zonisamide might be used in the treatment of both alcohol dependence and withdrawal syndrome (Sarid-Segal et al., 2009; Knapp et al., 2010; Rubio et al., 2010b), but the precise mechanism of this anti-alcoholic action has not yet been elucidated. Zonisamide and ethanol are characterized by a complex mechanism of action on the central nervous system. As both compounds regulate/modulate the activity of the same neurotransmitter systems. No data can be found in available literature regarding central interaction between ethanol and zonisamide. Greater knowledge of it may pave the way to searching its anti-alcoholic mechanism. Moreover, zonisamide has also important clinical significance due to using in various indications.

This study used a pharmaco-EEG method (QEEG), which is based on a quantitative analysis of changes in the EEG recordings from selected brain structures. It is one of the methods used to assess the character of interactions between drugs exerting a central effect and ethanol. Using QEEG, the results of our earlier studies have demonstrated that topiramate, oxcarbazepine and levetiracetam reduced the effect of ethanol on the bioelectric activity of the hippocampus and enhance its action in the frontal cortex and midbrain reticular formation. The present study was undertaken to determine whether the interaction between ethanol and zonisamide is...
similar in character. The effect of drug on hippocampus activity may be significant in the pathogenesis of addiction.

MATERIALS AND METHODS

Animals and treatment
Thirty rabbits (males and females) weighing 3.5–4.5 kg were used. The animals were housed in individual cages under normal laboratory conditions (20–22°C, 12 h light/12 h dark cycle) with free access to commercial chow and water. All experiments were performed between 08:00 a.m. and 04:00 p.m. Zonisamide (Eisai®) was given p.o. (in the form of a suspension in 1% methylcellulose solution) at a single dose of 20 or 60 mg/kg, or repeatedly at a dose of 30 mg/kg for 14 days. Because of its long half-life, this drug was administered once a day.

A 40.13% (v/v) solution of ethanol was injected as a bolus into the marginal ear vein at a dose of 0.8 g/kg 3 h after the administration of zonisamide. This dose of ethanol was selected on the basis of our previous studies (Pietrzak and Czarnecka, 2006, 2008, 2010). The control rabbits received (i.v.) isotonic saline solution or 1% methylcellulose (p.o.). The drugs were given in a volume of 0.2 ml/kg.

The experiments were carried out in strict accordance with Polish governmental regulations concerning experiments on animals (Dz.U.05.33.289). All the experimental protocols have been approved by the Local Ethical Committee for Experimentation on Animals (resolution No. 77/LB 587/2011).

Experimental procedure
Monopolar electrodes were implanted into the following rabbit brain structures: the midbrain reticular formation, MRF (P 8 mm, L 3 mm, H 15 mm); the dorsal hippocampus, Hp (P 3 mm, L 5 mm, H 5 mm); and the frontal cortex, C (A 3 mm, L 2 mm), according to Sawyer et al. (1954). The implantation was performed under butorphanol (0.1 mg/kg.), ketamine (10 mg/kg) and xylazin (0.5 mg/kg) anesthesia. The cortical electrodes were made of 0.15 mm diameter silver wire with a ball at the tip. The subcortical electrodes were made of 0.11 mm diameter Teflon-covered steel wire (Leico Industries, New York). Pharmaco-EEG experiments were performed 4 weeks after surgery.

EEG recordings were taken with an 8-channel electroencephalograph (Medicor-EEG 8S, Budapest, Hungary) with the time constant set at 0.3 s and the high filter set at 60 Hz. During the recordings, the animals remained in an observation cage (120×60×60 cm) with a transparent roof and front, and a grid floor. The cage was located in a quiet room, and a closed-circuit TV system was used to record the animals’ behavior.

One-minute artifact-free EEG recordings (selected by the experimenter) were taken for computer analysis. EEG samples were digitized at the rate of 128 samples/s, and the Fourier transform of consecutive 4 s epochs for each channel was calculated. Each spectrum consisted of 512 terms for a frequency range between 0 and 45 Hz, with each term having a width of 0.25 Hz. For further statistical analysis, the transformed data were compressed into these six frequency bands: 0.5–4 Hz (delta rhythm), 4–7 Hz (theta rhythm), 7–10 Hz (slow-alpha rhythm), 10–13 Hz (fast-alpha rhythm), 13–30 Hz (slow-beta rhythm), 30–45 Hz (fast-beta rhythm), and the absolute power over the entire frequency band (0.5–45 Hz) was calculated. The results are given as a percentage of these frequencies in the histogram. At the end of the experiment, the positions of the electrode tips were verified histologically.

Six animals were used for each experimental group. In acute experiments, the EEG was recorded before and 3 h after the administration of zonisamide, and at 15 and 60 min after the injection of ethanol. In the experiments involving multiple dosing, EEGs were recorded after 7 and 14 days of zonisamide treatment and at 15 and 60 min after the injection of ethanol.

Analysis of results
The results are presented as a percentage change of the initial value. The normality of the distribution was checked by the Kolmogorov–Smirnov test, with Lilliefors correction. Statistical analysis was performed with the Kruskal–Wallis (ANOVA) test and the Mann–Whitney U-test (comparison between groups), or the Wilcoxon matched pair test (comparison in a group), using the Statistics for Windows 5.0 software package. A P-value of 0.05 or less is considered to indicate a statistically significant difference for all statistical tests.

RESULTS

The mean contribution of particular frequencies to the total power spectrum (histogram) is given in Table 1. No change was found in EEG recordings in rabbits who received intravenously 0.9% (w/v) NaCl (Fig. 1A) or 1% methylcellulose (data not shown). The control group in present work (Fig. 1A) was determined during several earlier series of experiments, which increased its “statistical power” (14 animals) and it has only a nature of information. However, data contained in Table 1 were calculated based on current experiment. Intravenous injection of ethanol (0.8 g/kg) markedly changed EEG recordings from the frontal cortex (C) and the midbrain reticular formation (MRF), and—to a lower extent—from the dorsal hippocampus (Hp) (Fig. 1B and C). An increase in the power in the 0.5–4 Hz frequency band and a decrease in the 4–7, 7–10 and 30–45 Hz frequency bands from the C and the MRF recordings and in the 13–30 Hz frequency band (C recording only) were observed. An analysis of the EEG recordings from Hp revealed an increase in the power in the 0.5–4 Hz frequency range and a decrease in the 30–45 Hz frequency band. In all studied structures, an increase in the absolute power was

<table>
<thead>
<tr>
<th>Frequencies (Hz)</th>
<th>MRF (%) ± SD.</th>
<th>Hp (%) ± SD.</th>
<th>C (%) ± SD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–4</td>
<td>32.16 ± 5.21</td>
<td>31.91 ± 4.11</td>
<td>30.01 ± 4.47</td>
</tr>
<tr>
<td>4–7</td>
<td>33.58 ± 6.56</td>
<td>34.21 ± 5.89</td>
<td>34.68 ± 6.65</td>
</tr>
<tr>
<td>7–10</td>
<td>15.38 ± 3.13</td>
<td>15.96 ± 3.23</td>
<td>16.52 ± 4.15</td>
</tr>
<tr>
<td>10–13</td>
<td>11.45 ± 2.03</td>
<td>11.95 ± 3.78</td>
<td>10.98 ± 2.76</td>
</tr>
<tr>
<td>13–30</td>
<td>5.27 ± 1.67</td>
<td>4.89 ± 1.34</td>
<td>5.45 ± 1.83</td>
</tr>
<tr>
<td>30–45</td>
<td>2.16 ± 0.35</td>
<td>2.06 ± 0.74</td>
<td>2.36 ± 0.41</td>
</tr>
</tbody>
</table>

MRF, midbrain reticular formation; Hp, dorsal hippocampus; C, frontal cortex.
Fig. 1. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of saline (Sal) (A) and 15 and 60 min after ethanol of 0.8 g/kg i.v. (Et15) (B); (Et60) (C); (1) 0.5–4 Hz; (2) 4–7 Hz; (3) 7–10 Hz; (4) 10–13 Hz; (5) 13–30 Hz; (6) 30–45 Hz; (1–6) 0.5–45 Hz; (MRF) midbrain reticular formation; (Hp) hippocampus; (C) frontal cortex. Significant difference vs. initial value, *P < 0.05, Wilcoxon’s test.
found (Fig. 1B and C). A marked increase of the amplitude was found in the visual assessment of post-ethanol recordings. The changes persisted for a 1 h-long observation.

No changes in the behavior were observed after acute or chronic administration of zonisamide. In contrast, immediately after the injection of ethanol, the rabbits exhibited considerable disturbances of their body balance, which subsided gradually, and finally disappeared after 45–60 min.

Zonisamide given p.o. to rabbits at a single dose of 20 mg/kg slightly changed the EEG recordings from the brain structures. An increase in the proportion of 0.5–4 Hz (Hp recording), with a decreased proportion of 4–7 Hz, 7–10 Hz (Hp recording) and 30–45 Hz frequencies (MRF recording), was observed (Fig. 2A). Zonisamide (20 mg/kg) did not modify the effect of ethanol on the EEG recordings from the frontal cortex (Fig. 2A).

Zonisamide (20 mg/kg) administered to rabbits 3 h before ethanol (0.8 g/kg) did not significantly affect the post-ethanol changes in the EEG. Changes after 15 and 60 min did not differ significantly from those found in the animals receiving ethanol alone (Fig. 2B and C).

Zonisamide administered p.o. to rabbits at the high dose of 60 mg/kg changed the EEG recordings from hippocampus and midbrain reticular formation. The most pronounced changes were observed in the hippocampus. The proportion of the low frequency (0.5–4 Hz) increased, whereas the proportion of 7–10, 10–13, 13–30 and 30–45 Hz frequencies decreased. In recordings obtained from the MRF, zonisamide decreased the proportion of 7–10 and 30–45 Hz frequencies. Zonisamide did not significantly affect the spectrum of the EEG recording from the frontal cortex. By comparing the EEG recordings after administration of zonisamide at doses of 20 and 60 mg/kg, pronounced changes were observed after higher dose (Fig. 3A).

Zonisamide (60 mg/kg) administered to rabbits 3 h before ethanol (0.8 g/kg) enhanced the effect of ethanol on the EEG recordings in all studied structures, compared with the action of ethanol alone. In recordings from 15 min after administration, an enhanced effect of ethanol on low frequency (0.5–4 Hz), accompanied by decreased proportion of other studied frequencies, was observed (Fig. 3B). One hour after injection of ethanol, these changes in the EEG recordings had become less pronounced and did not affect all studied frequencies. The increase of the 4–7 Hz frequency proportion was observed in Hp compared to the recording after ethanol alone (Fig. 3C).

Zonisamide administered to rabbits at a dose of 30 mg/kg/day for 7 days slightly altered the EEG recordings obtained from all structures (Fig. 4A). Changes observed in the MRF involved an increased proportion of the 4–7 Hz frequency and a decreased proportion of the 30–45 Hz frequency. No effect of zonisamide on the EEG recordings was observed in the C and Hp (Fig. 4A).

After 7 days of administration, zonisamide significantly decreased the depressive effect of an acute dose of ethanol on the EEG recordings in all studied structures. After 15 min from administration of ethanol, inhibition of the ethanol-induced increase of low frequencies (0.5–4 Hz) was observed in all studied structures. A reduction of the ethanol-induced decrease of frequencies in the 4–7 Hz band was also recorded in MRF and C. Furthermore, a beneficial decrease of ethanol-induced changes (10–13 Hz) was observed in the frontal cortex (Fig. 4). After 45–60 min from administration, the EEG changes were mostly visible (Fig. 4B and C).

After 14 days of zonisamide administration, changes in EEG recordings were similar to these observed after the first week of treatment, but they were more pronounced (Fig. 5A). In all studied structures, a decreased proportion of 0.5–4 Hz frequencies and an increased proportion of 7–10 Hz frequencies was observed. The EEG recorded from the C and MRF also demonstrated an increased proportion of the 4–7 Hz frequency band. In the recording obtained from C, zonisamide enhanced the proportion of 10–13 Hz range (Fig. 5A).

Zonisamide administered for 14 days decreased ethanol-induced alterations in the EEG recordings in all studied structures. Zonisamide prevented the ethanol-induced increase of 0.5–4 Hz and decrease 4–10 Hz frequencies. Furthermore, zonisamide affects beneficial inhibition in the highest frequency band (30–45 Hz) in the Hp, which ethanol alone significantly reduced. The EEG recorded from the C demonstrated a similar, beneficial effect on 10–13 Hz range (Fig. 5).

These alterations were observed during the acute phase of ethanol action (5–15 min after administration) and most of them were also visible after 45–60 min from ethanol administration (Fig. 5B and C).

DISCUSSION

This study used a pharmaco-EEG method to assess the effect of zonisamide and ethanol on the bioelectric activity of rabbit brains. Ethanol produces characteristic, dose-dependent changes in the EEG recordings, which are more pronounced when its blood concentration rises rapidly. The present results demonstrated that ethanol administered to rabbits as a single high dose potentely altered pattern of EEG recorded from the frontal cortex and, to a slightly smaller extent, the recordings from the midbrain reticular formation and the hippocampus. The observed changes were associated with the increased proportion of delta rhythm in the recordings, and the reduced proportion of fast-beta rhythm, theta rhythm, slow-alpha rhythm and slow-beta rhythm. These changes in the EEG spectrum are associated with the potent depressive effect of ethanol on the central nervous system. The increased depressive effect on central functions is the main risk of an interaction between alcohol and drugs and can lead to respiratory depression, which is life threatening.

Zonisamide alone significantly altered the EEG recordings in the hippocampus. A single dose of the drug caused an increased proportion of delta rhythms and decreased the proportion of theta and alpha rhythms. The changes observed in MRF were associated with the decreased proportion of fast-beta and also alpha rhythms after high dose.

Zonisamide administered as a single high dose together with ethanol significantly enhanced the ethanol-induced changes in the EEG recordings from all studied structures, especially in the acute phase of the action of ethanol. After 60 min of administration, a gradual disappearance of the depressive effect of the zonisamide on bioelectrical activity was observed in all studied structures, especially in the delta frequency range.

The mechanism of this interaction is dose-dependent and may be related to the effect on ion channels and neurotransmitter release. Preclinical studies showed that zonisamide reduces sodium currents to the neuronal cell body. This raises the threshold for action potentials and reduces neuronal excitability. Zonisamide has also been shown to inhibit low-threshold
Fig. 2. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD 180 min after administration of zonisamide at 20 mg/kg p.o. (ZN20_180) (A) and 15 and 60 min after ethanol 0.8 g/kg i.v. (ET15, ET60) (B and C). Significant difference vs. initial value, *P < 0.05, Wilcoxon's test. Significant difference vs. ethanol-treated group, ‡P < 0.05, Kruskal–Wallis test. For explanation of numbers and brain structure abbreviations see legend of Fig. 1.
Fig. 3. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD 180 min after administration of zonisamide at 60 mg/kg p.o. (ZN60_180) (A) and 15 and 60 min after ethanol 0.8 g/kg i.v. (ET15, ET60) (B and C). Significant difference vs. initial value, \( ^aP<0.05 \), Wilcoxon’s test. Significant difference vs. ethanol-treated group, \( ^bP<0.05 \), Kruskal–Wallis test. For explanation of numbers and brain structure abbreviations see legend of Fig. 1.
Fig. 4. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of zonisamide at 30 mg/kg p.o. (ZN30 for 7 days) (A) and 15 and 60 min after ethanol at 0.8 g/kg i.v. (ET) (B and C). Significant difference vs. initial value, *P < 0.05, Wilcoxon’s test. Significant difference vs. ethanol-treated group, †P < 0.05, Kruskal–Wallis test. For explanation of numbers and brain structure abbreviations see legend of Fig. 1.
T-type Ca\(^{2+}\) channels in cultured neurons of rat cerebral cortex, leading to a reduction in action potential, although the drug may indirectly mediate neurotransmitter release through the effects on Na\(^{+}\) and Ca\(^{2+}\) (Miwa and Kondo, 2011; Brodie et al., 2012). Ethanol administered as a high dose inhibits ion channels, especially calcium channels and as consequence
significantly inhibits the release of neurotransmitters (Theile et al., 2009).

Changes in EEG recordings after repeated administration of zonisamide are different from those, which were observed after a single dose. Zonisamide administered in multiple doses caused the shift of the spectrum toward fast rhythms. In studied structures, a significantly decreased proportion of delta rhythms and an increased proportion of theta and alpha rhythms were observed. These changes were observed after 7 days of treatment and they were significant after 14 days of treatment. The above data demonstrate an activating effect in the studied structure.

In available literature, little data can be found about the effect of zonisamide on EEG recording in patients. Infantile spasms is a disease with a characteristic EEG pattern called hypsarrhythmia, and this syndrome is usually resistant to conventional AEDs. After treatment with zonisamide, some children respond to drug therapy with the disappearance of hypsarrhythmia (Lotze and Wilfong 2004; Yum and Ko, 2009). On the other hand, the EEG recordings of a 14-year-old patient with epilepsy and tuberous sclerosis showed the immediate appearance of low frequency (3–3.5 Hz) in the frontal cortex after the onset of seizures. After 11 days of zonisamide treatment, the seizures had disappeared (Seki et al., 2004).

In our study, a beneficial effect of repeatedly administered zonisamide on ethanol-induced EEG changes was observed and this effect was demonstrated especially in the hippocampus. In recordings obtained from this structure, an inhibition of the ethanol-induced changes in theta rhythm was observed. Ethanol alone significantly reduced the proportion of the theta rhythm in the EEG recordings from all studied structures. This may be correlated with a deterioration of the cognitive and memory processes.

Zonisamide administered in multiple doses for 7 days significantly decreased the depressive effect of an acute dose of ethanol on the EEG recordings. Alterations were observed in the acute phase of the action of the ethanol, and they persisted mostly throughout the 1 h-long observation. The drug prevented ethanol-induced changes and reduced the proportion of delta and theta rhythms. Alpha rhythms were also inhibited in the frontal cortex. After a 14-day period of treatment, the effect was enhanced. In addition, the EEG recorded from the Hp demonstrated inhibited changes in the proportion of beta rhythms which the ethanol had significantly reduced.

The beneficial effect on recordings from the hippocampus deserves special attention. In our study, particularly important is the observation that repeatedly administered zonisamide significantly reduced hippocampal sensitivity on the action of ethanol. In the available literature, a negative effect of chronic ethanol administration on the function of the central nervous system (CNS) has been mainly emphasized. However, a central effect of a single dose of ethanol cannot be neglected, particularly the effect of high doses of ethanol. It has been shown that particular areas of the CNS are variably exposed to damage by acute or chronic ethanol, and this effect depends on ethanol doses, age and individual sensitivity. Acute and chronic ethanol administration may cause significant changes, which occur mainly in the cerebral cortex, cerebellum and hippocampus (Matthews and Morrow, 2000; Jaatinen and Rintala, 2008). Acute ethanol administration degraded the spatial sensitivity of hippocampal place cells and impaired cognitive processes, affecting both spatial memory and spatial learning. Chronic alcohol exposure also impaired spatial cognition and significantly altered hippocampal neurochemistry and neuroanatomy (Matthews and Morrow, 2000). In recent years, memory processes are associated with addiction development and therefore the role of the hippocampus has been underlined in the pathogenesis of addiction. Cognitive processes and the adaptive changes leading to addiction are based on common cellular mechanisms which are involved in memory and the learning process (Canales, 2013). A beneficial nature of an interaction between zonisamide and a high single dose of ethanol certainly does not exclude another character of an interaction with chronic alcohol, and there is a need to broaden research in this regard. Previous experimental studies have demonstrated that zonisamide decreased ethanol consumption in mice and rat limited access models of drinking; however, the mean ethanol intake was not significantly different between the post-treatment phase and the baseline period (Knapp et al., 2007). The results of initial clinical trials are positive but require further studies. It has been shown that zonisamide, used in an appropriate dose, reduced the quantity of ethanol self-administered by risky drinkers (Sarid-Segal et al., 2009). Arias et al. (2010) have demonstrated that 12-week administration of zonisamide reduced the number of heavy drinking days and drinks per week in addicts (Arias et al., 2010). It has also been proved that zonisamide attenuated withdrawal syndromes, and reduced craving and anxiety more than diazepam in patients with alcohol dependence disorder (Rubio et al., 2010b). However, further studies are necessary to confirm efficacy and develop an optimal therapeutic model (Knapp et al., 2010; Rubio et al., 2010a).

In the available literature, several authors have described the neuroprotective activity of zonisamide. Hitherto, most studies have been about the effect on hypoxic neuronal damage and the authors have emphasized that zonisamide reduced damage in the treatment of ischemic cerebral damage (Hayakawa et al., 1994; Minato et al., 1997; Costa et al., 2011). In an animal model of ischemia, Noda et al. (1999) have demonstrated that zonisamide inhibits degeneration of the pyramidal cells in the hippocampus. It cannot be excluded that the effect observed in our study may also be result of the neuroprotective activity of zonisamide, particularly in the hippocampus. The effect was pronounced in the hippocampus because ethanol-induced changes were inhibited in the spectrum of EEG recordings, at both slow and fast frequencies. As is apparent from the available literature, an acute high dose of ethanol may result in neurodegeneration and induces oxidative stress which leads to formation of the free radicals and cerebral metabolic disorders (Mansouri et al., 2001). It has also been shown that acute intracerebellar administration of ethanol decreased the amount of extracellular GABA and increased the NMDA-induced production of NO in rats, which may be a possible excitotoxic mechanism in the cerebellar nuclei (Manto et al., 2005). Furthermore, acute ethanol administration also caused apoptotic neurodegeneration in the developing central nervous system of animals (Young and Olney, 2006).

In summary, zonisamide administered in a high single dose significantly enhanced the ethanol-induced changes in the EEG recordings. The nature of observed changes demonstrated that zonisamide and ethanol have synergistic and inhibitory effects on the CNS. The serious risk may be an acute ethanol intoxication during administration of zonisamide at high doses due to exacerbation of the central effects of ethanol. In contrast,
zonisamide decreased ethanol-induced changes in the rabbits’ EEG recordings, particularly the hippocampus, after multiple administrations. The effect of zonisamide on the hippocampus may be result of a neuroprotective effect which may be important in the anti-alcoholic mechanism of zonisamide. However, it is necessary to broaden knowledge in this regard and carry out further research.

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