# 2.5 Clinical overview

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## List of Abbreviations

| | | |
|---|---|---|
| AED | : | Antiepileptic Drug |
| ATC | : | Anatomical Therapeutic Chemical Classification System |
| AUC | : | Area Under Curve |
| $AUC_{0-72}$ | : | Area Under Curve Truncated to 72 hours |
| BMI | : | Body Mass Index |
| CAE | : | Childhood absence epilepsy |
| CDSCO | : | Central Drug Standard Control Organization |
| Cmax | : | Maximum Plasma Concentration |
| CNS | : | Central Nervous System |
| CV | : | Coefficient of Variation |
| ECG | : | Electrocardiogram |
| EEG | : | Electroencephalography |
| EMEA | : | European Medicines Evaluation Agency. |
| GTCs | : | Generalized tonic-clonic seizures |
| Hr | : | Hour |
| HCV | : | Hepatitis C Virus |
| HIV | : | Human Immunodeficiency Viruses |
| HQC | : | Higher Quality Control |
| ICH | : | International Conference on Harmonization |
| ICMR | : | Indian Council of Medical Research |
| ISTD | : | Internal Standard |
| Kg | : | Kilogram |
| LCMS/MS | : | Liquid Chromatography-Tandem Mass Spectrometry |
| LLOQ | : | Lower Limit of Quantification |
| LMQC | : | Lower Middle Quality Control |
| Ln | : | Log transformed |
| LQC | : | Lower Quality Control |
| Mg | : | Milligram |
| mL | : | Millimeter |
| MQC | : | Middle Quality Control |

| | | |
|---|---|---|
| N | : | Number of Subjects |
| ng | : | Nanogram |
| NSAID | : | Non-Steroidal Anti Inflammatory Drug |
| OTC | : | Over The Counter |
| P/A | : | Posterior Anterior View |
| PAR | : | Public Assessment Report |
| QC | : | Quality Control |
| R | : | Reference Product |
| RCF | : | Relative Centrifugal Force |
| SAS | : | Statistical Analytical System |
| SD | : | Standard Deviation |
| SOP | : | Standard Operating Procedure |
| SPC | : | Summary of Product Characteristics |
| T | : | Test Product |
| Tmax | : | Time to reach maximum plasma concentration |
| UK | : | United Kingdom |
| ULOQ | : | Upper Limit of Quantification |
| USA | : | United States of America |
| µg | : | micrometre |
| % | : | Percentage |
| ® | : | Registered Trademark |
| ºC | : | Degree Celcius |

# 2.5 CLINICAL OVERVIEW

## 2.5.1 PRODUCT DEVELOPMENT RATIONALE

Ethosuximide is one of three succinimides used as anticonvulsants, the other two are: methsuximide (*N*-2-dimethyl-2-phenylsuccinimide) and phensuximide (*N*-methyl-2-phenylsuccinimide). The structure of ethosuximide contains a five-membered ring with two negatively charged carbonyl oxygen atoms. The anticonvulsant effect of the drug is attributed to the "ring nitrogen" situated between the two groups. The drug exists as a racemic mixture of two separate enantiomers because of a chiral carbon at position two of the succinimide ring. [redacted]

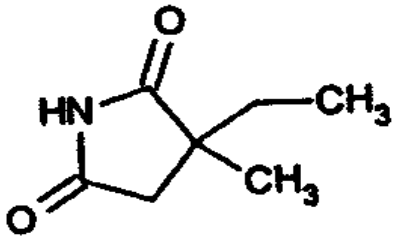
[redacted]

Properties

Chemical name: 3-ethyl-3-methyl-2, 5-pyrrolidinedione, 3-ethyl-3-methyl-, (±)-.

Molecular formula: $C_7H_{11}NO_2$

Structure:




Molecular weight: 141.17

[redacted]

**Therapeutic Indications:**

Ethosuximide 250 mg/5 ml oral solution is indicated in the following conditions:

- Pyknoleptic absences as well as complex and atypical absences.
- Myoclonic-astatic petit mal and myoclonic fits of adolescents (impulsive petit mal), if other medicinal products are not effective and/or are not tolerated.

**Legal Aspects**

The product Ethosuximide 250 mg / 5 mL Oral Solution of [redacted]

[redacted]

This clinical overview is intended to be a concise document that critically analyses the existing literatures on Ethosuximide. For the preparation of this clinical overview, a search for published literatures was carried out using pubmed, medlines etc as a primary source.

## 2.5.2 OVERVIEW OF BIOPHARMACEUTICS

The applicant has performed a bioequivalence study between the test product Ethosuximide 250 mg / 5 mL Oral Solution and reference product Zarontin® (Ethosuximide 250 mg/5mL Sirop 200 mL) in healthy, adult, human subjects under fasting conditions.

[redacted]

Study Title:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Ethosuximide 250 mg / 5 mL Oral Solution of [redacted] Zarontin® (Ethosuximide 250 mg/5mL Sirop 200 mL) [redacted] in normal, healthy, adult, human subjects under fasting condition.

Study Design:

An open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study in normal, healthy, adult, human subjects under fasting condition.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Pharmacokinetic Results:

Descriptive Statistics of Formulation Means for Ethosuximide [redacted]

| **Parameters (Units)** | **Mean ± SD (untransformed data)** | |
|---|---|---|
| | **Test Product-T** | **Reference Product-R** |
| $T_{max}$ (h)[#] | 1.834 (0.333 - 5.000) | 1.509 (0.333 - 6.000) |
| $C_{max}$ (ng/mL) | 7122.767 ± 1630.8232 | 6937.110 ± 1101.5533 |
| $AUC_{0-72}$ (ng.h/mL) | 300402.136 ± 33852.8360 | 296181.026 ± 32625.1400 |

[#]$T_{max}$ is represented as median (min-max) value.

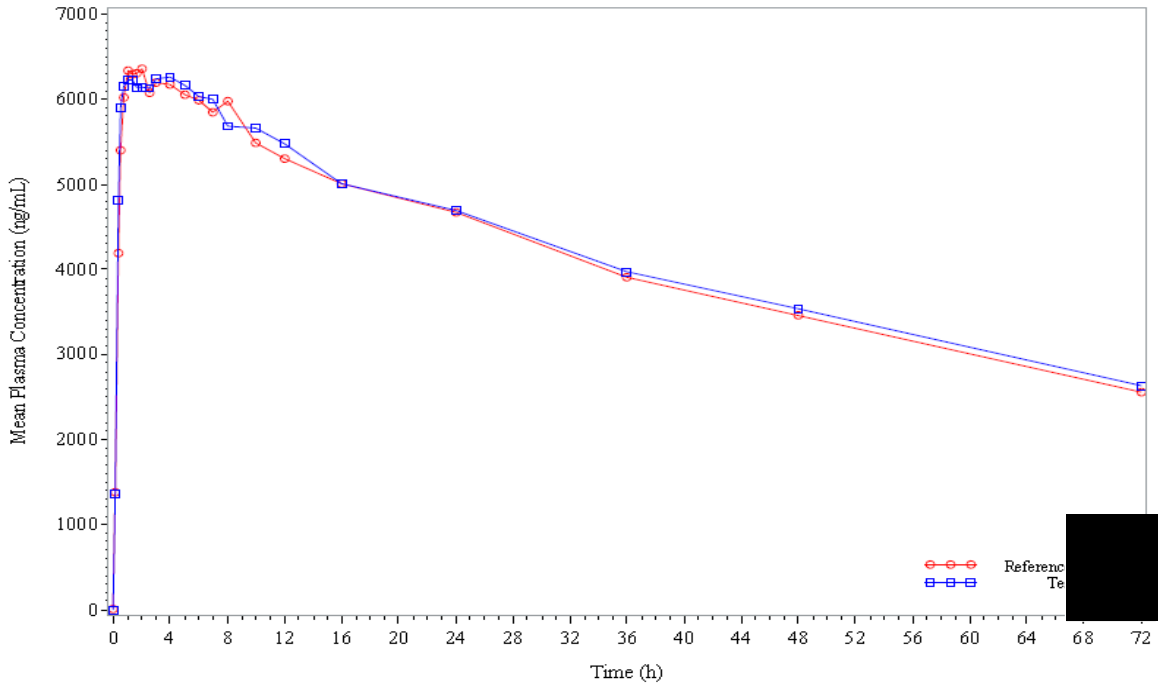
Statistical Results

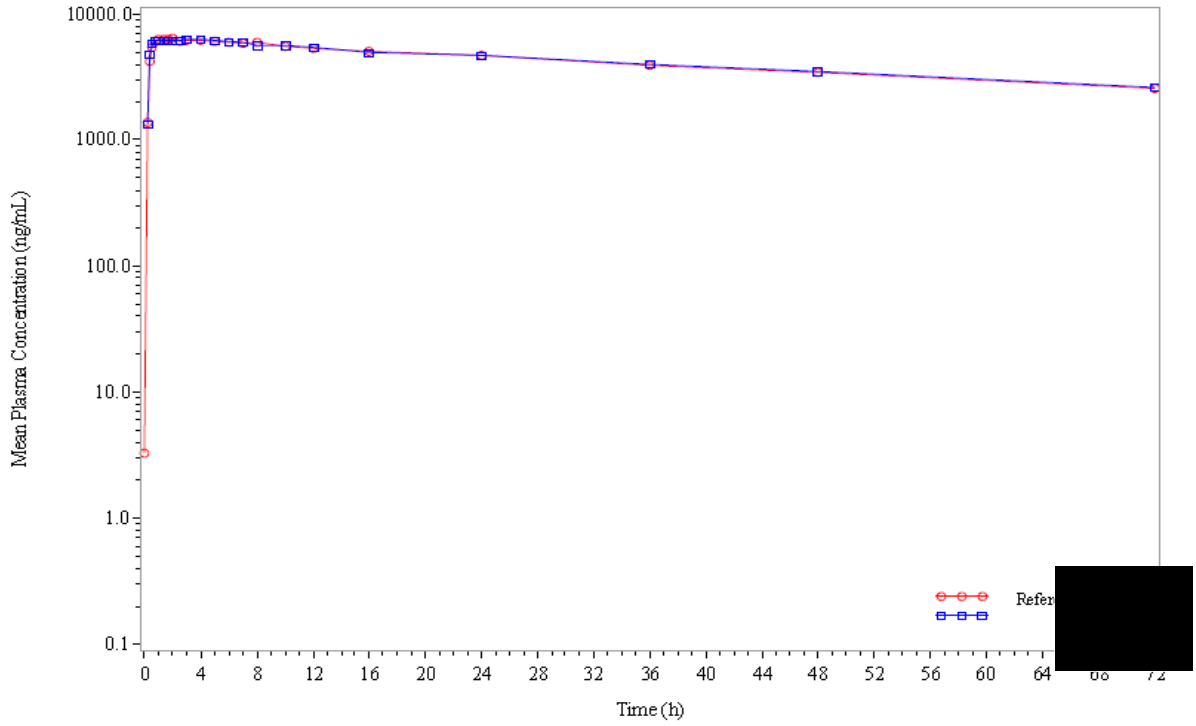
Geometric Least Square Means, Ratio, 90% Confidence Interval, Intrasubject Variability and Power for Ethosuximide (N = 16)

| Parameters | Geometric Least Squares Means | | | 90%Confidence Interval | Intra Subject CV (%) | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product - T | Reference Product - R | Ratio (T/R) % | | | |
| $lnC_{max}$ | 6980.008 | 6859.667 | 101.8 | 96.29 - 107.52 | 8.9 | 100.0 |
| $lnAUC_{0-72}$ | 298635.855 | 294546.620 | 101.4 | 98.85 - 103.99 | 4.1 | 100.0 |

Mean plasma concentration vs. time curve for Ethosuximide

(Upper panel: Linear plot; Lower panel: Semi log plot






Safety Results

[redacted] enrolled subjects were included in safety assessment.

Subjects were monitored for adverse events throughout the study.

During the study, no any adverse event was reported with test and reference product.

The test and reference products were comparable in their safety and tolerability, hence the test product was found to be safe and well tolerated upon single dose administration in healthy, adult human male subjects.

Study Conclusion

The 90% confidence intervals for the test/reference ratios of the geometric least squares means between test and reference formulations calculated for $C_{max}$ and $AUC_{0-72}$ were within the bioequivalence acceptance limits for ethosuximide. Based on the results obtained, it is concluded that Ethosuximide 250 mg / 5 mL Oral Solution of [redacted] is bioequivalent to Zarontin® (Ethosuximide 250 mg/5mL Sirop 200 mL) of Essential [redacted] in normal, healthy, adult, human subjects under fasting condition.

## 2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Anti-epileptics, succinimide derivatives

ATC code: N03AD01

[redacted]

### *2.5.3.1 Mechanism of Action*

Ethosuximide blocks voltage-dependent sodium channels and reduces calcium currents through T-type channels. Also, ethosuximide at therapeutic concentrations enhances both, dopaminergic and serotonergic neurotransmission and inhibits glutamate-induced excitation. The drugs also share a very unique mechanism among antiepileptic drugs – it apparently reduces the overproduction of nitric oxide and free radicals, which may be related to its anticonvulsant and neuroprotective effects. [redacted]

Ethosuximide has a narrow clinical spectrum—it suppresses absence seizures, but not generalized tonic–clonic seizures or focal onset seizures. The available evidence suggests that the main mechanism of action of Ethosuximide is blockade of transient, low-threshold calcium currents produced by T-type calcium channels in thalamic neurons, thereby preventing the synchronized firing of corticothalamic neurons that produce the spike wave discharges of absence seizures. [redacted]

### *2.5.3.2 Pharmacodynamics*

Ethosuximide is an anti-epileptic of the class of succinimides that apparently exerts multiple mechanisms of action. The activity of ethosuximide in absence type epilepsy seems to rely primarily on the inhibition of T-type calcium channels in the thalamus.

<u>Children and adolescents</u>

In a double-blind, randomised study of 20 weeks duration in 453 children aged 2.5 to 13 years with newly diagnosed childhood absence epilepsy, the efficacy, tolerance and neuropsychological effects of ethosuximide, valproic acid and lamotrigine as monotherapy in childhood absence epilepsy were studied. Those treated with either ethosuximide or valproic acid had higher freedom-from-failure rates (53% and 58%, respectively) than those given lamotrigine (29%, odds ratio with ethosuximide vs. lamotrigine, 2.66; 95% confidence interval [CI], 1.65 to 4.28; odds ratio with valproic acid vs. lamotrigine, 3.34; 95% CI, 2.06 to 5.42). In both pre-specified and post-hoc analyses, ethosuximide resulted in fewer attentional effects as compared

with valproic acid (at weeks 16 and 20, the percentage of test subjects with a confidence index score of 0.60 or higher in the Conners' Continuous Performance Test was greater in the valproic acid group than in the ethosuximide group [49% vs. 33%] and the lamotrigine group [49% vs. 24%).

[redacted]

[redacted] characterized the pretreatment behavioral problems and differential effects of initial therapy in children with childhood absence epilepsy (CAE). The Child Behavior Checklist was administered at baseline, week 16–20, and month 12 visits of a randomized double-blind trial of ethosuximide, lamotrigine, and valproate. A total of 382 participants at baseline, 310 participants at the week 16–20 visit, and 168 participants at the month 12 visit had Child Behavior Checklist data. At baseline, 8% of children with CAE had elevated total problems scores. At week 16–20, participants taking valproic acid had significantly higher total problems, externalizing problems, attention problems and attention-deficit/hyperactivity problems scores compared to participants taking ethosuximide. Lack of seizure freedom and elevated week 16–20 Conner Continuous Performance Test confidence index were associated with worse total problems scores. At month 12, participants taking valproic acid had significantly higher attention problems scores compared to participants taking ethosuximide. Results conclude that pretreatment and ongoing behavioral problems exist in CAE. Valproic acid is associated with worse behavioral outcomes than ethosuximide or lamotrigine, further reinforcing ethosuximide as the preferred initial therapy for CAE. [redacted]

[redacted] investigated the cognitive profile of ethosuximide. Using a cross-sectional study, investigators used an extensive neuropsychological test battery in patients with epilepsy aged 6–16 years who were treated with monotherapy ethosuximide and also evaluated the efficacy of the drug by seizure frequency (seizure free or not). Sixty one patients with a mean age of 9.4 years were enrolled who used on average 686 mg/day ethosuximide as monotherapy. Ethosuximide was effective in the majority of the patients (70% were seizure free for at least 6 months at moment of inclusion). The total study population showed impairments of intelligence, visuomotor, and attentional function including activation/alertness. Comparisons between the well-controlled patients and patients who were not in remission showed significantly lower intelligence values and lower performance on the visual-perceptual and attentional tasks for the group with ongoing seizures. Results suggested that the higher order cognitive dysfunctions (such as intelligence and visual-perceptual functions) may be regarded as seizure or aetiology effects and that the impaired fluid cognitive functions, such as activation/alertness, sustained auditory attention and attentional control or switching, were due to ethosuximide. This study suggests the attentional dysfunction resulting in psychomotor slowing and alertness deficits may be regarded as effects of ethosuximide. Although no untreated baseline assessment was

available, these effects are comparable to those of other AEDs, and ethosuximide may therefore be considered an AED with only mild effects on cognition. [redacted]

### *2.5.3.3 Pharmacokinetics*

Ethosuximide is clinically available for oral administration in the form of syrup or capsules. It is rapidly and almost completely absorbed when given orally to either children or adults; the syrup is absorbed at a faster rate. The bioavailability of ethosuximide is 95–100%. The volume of its distribution has been reported as 0.7 L/kg in either children or adults. Ethosuximide is not bound to plasma proteins and its levels in cerebrospinal fluid, saliva, or tears are similar to those in plasma. [redacted]

In healthy adult males, the peak plasma levels of ethosuximide reached 15 µg/ mL at 3–5 hours after a single 750 mg oral dose of the drug and remained at this level for 24 hours. Ethosuximide is clinically effective at plasma levels ranging from 40 to 100 mg/L (300–700 µmol/L), but in some patients levels of up to 150 mg/L (1000 mmol/L) are required and tolerated if achieved by slow titration. In nursing infants, serum levels are maintained between 15 and 40 mg/L. Due to its linear kinetics, the plasma levels of ethosuximide increase in proportion to increasing doses. Seven to 12 days are required to reach steady-state plasma levels of ethosuximide. [redacted]

Public Assessment Report:

Bioequivalence study of ethosuximide after single dose administration (fed conditions) of Ethosuximid [redacted] was conducted in 24 healthy subjects. Twenty-four (24) subjects were planned for enrolment and were dosed in period 1 at the beginning of the study. Twenty-two (22) subjects completed the clinical portion of the study and were considered for Pharmacokinetic and Statistical analysis.

| Treatment | $AUC_{0-72}$ ng/ml/h | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| Test | 252802.3 ± 49336.18 | 5882.9 ± 906.45 | 1.74 (0.33 – 3.67) |
| Reference | 249529.0 ± 47146.15 | 5522.8 ± 862.56 | 2.32 (0.67 – 5.00) |
| *Ratio (90% CI) | 101.23 (99.57 – 102.92) | 106.55 (102.03 – 111.27) | |

$AUC_{0-72}$ can be reported instead of $AUC_{0-t}$, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$C_{max}$ Maximum plasma concentration

$t_{max}$ Time until Cmax is reached

The results of this study show that for extent of absorption (AUC) and the rate of absorption (Cmax) the 90 % confidence intervals are within the acceptance range of 80.00 % - 125.00 % for ethosuximide and hence bioequivalence was demonstrated between the test and reference product.

[redacted]

In the population studies, the 'relation between plasma ethosuximide level and drug dose tended to become steeper in the same subjects when higher doses for each subject were considered (figures below).

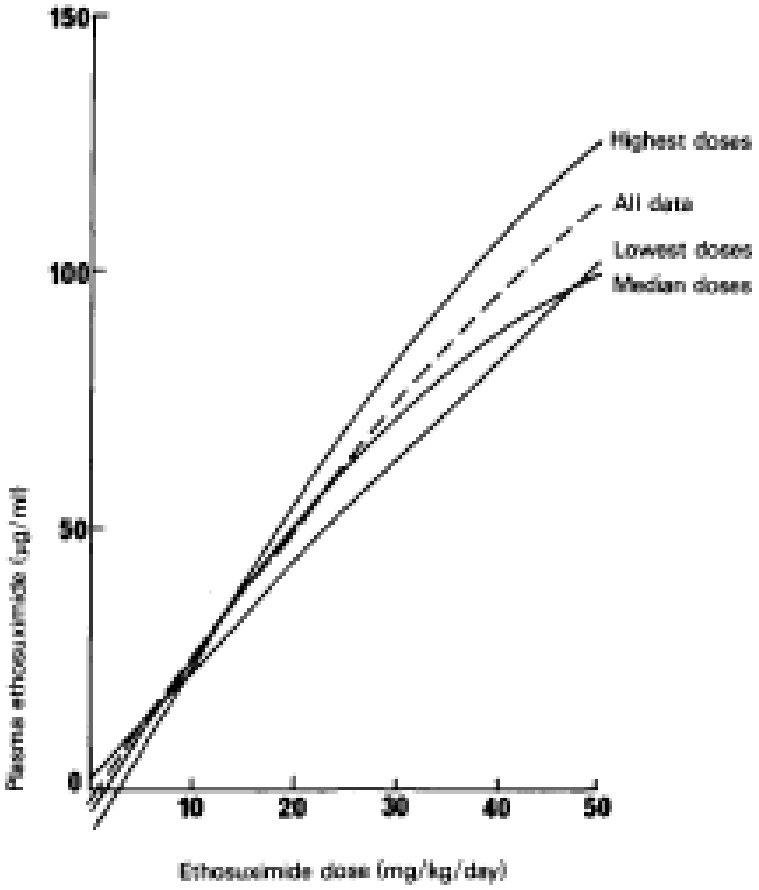



Figure 01: Parabolic regression lines for the plot of steady-state plasma ethosuximide levels against drug dose for all the doses taken by each patient, and for the highest, lowest and median doses taken by each patient.

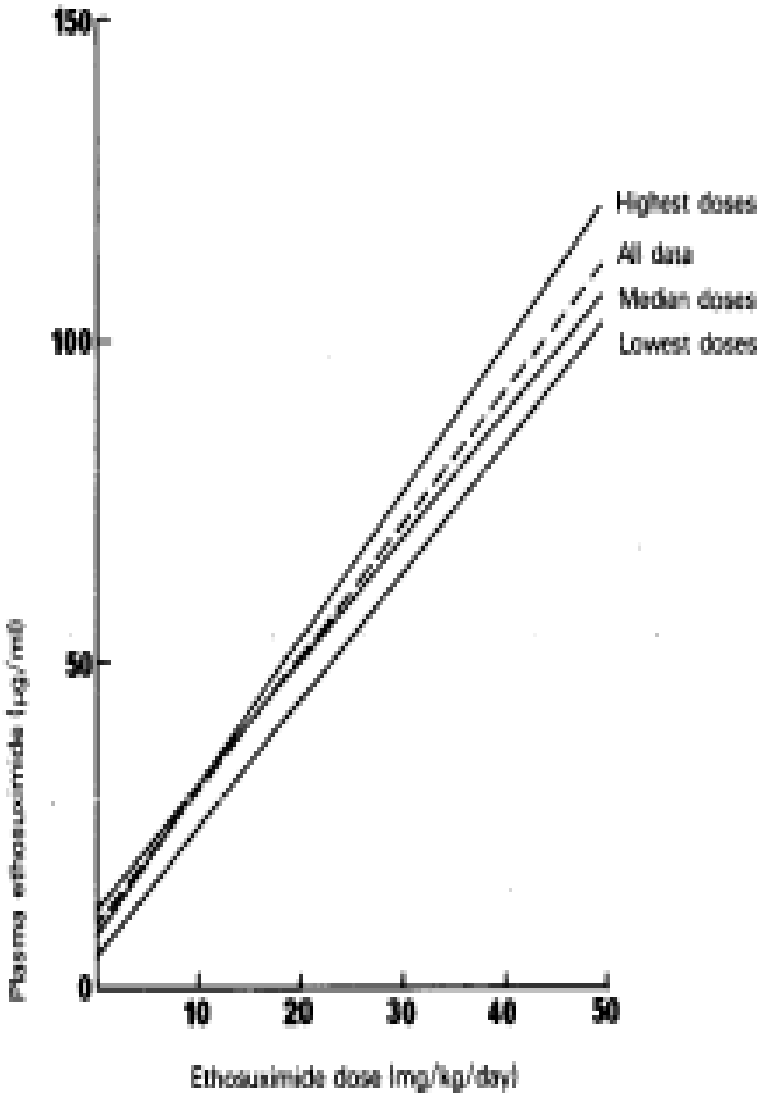



Figure 02: Linear regression lines for the plot of steady-state plasma ethosuximide levels against drug dose for all doses taken by each patient and for the highest, lowest and median doses taken by each patient.

[redacted]

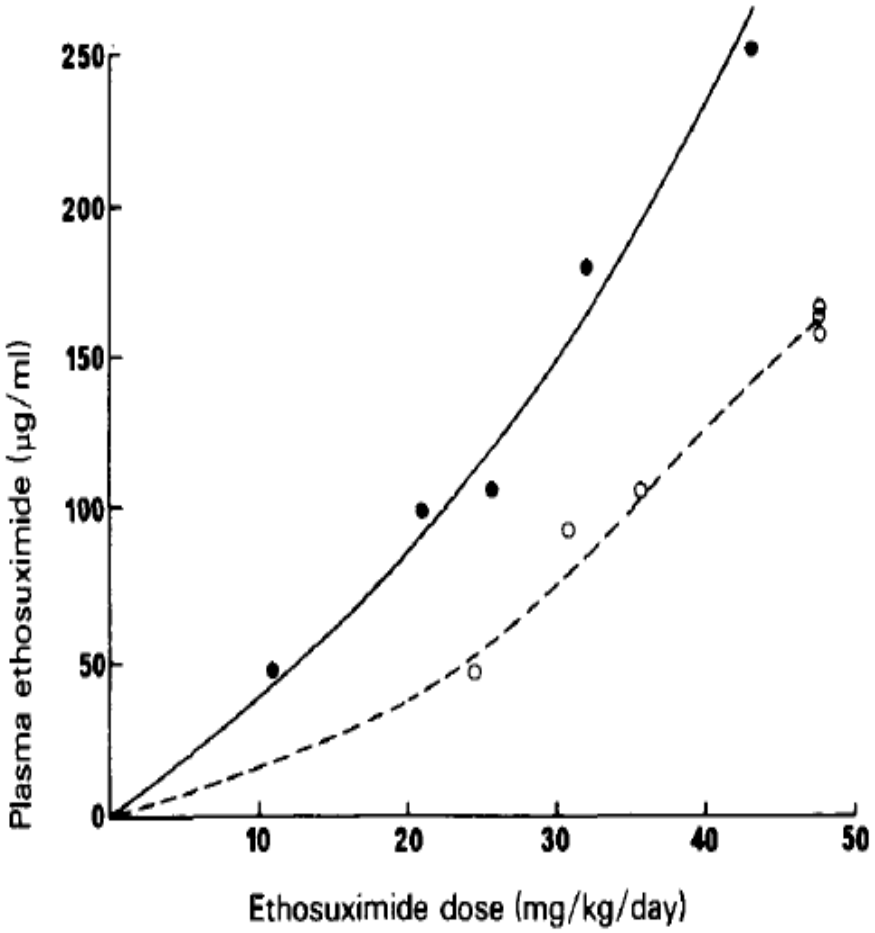



Figure 03: The curvilinear relation between steady-state plasma ethosuximide level and drug dose in 2 patients.

In these subjects, the relation appears curved rather than rectilinear. In view of this finding, a linear regression for plasma level on dose was calculated for each of the 9 subjects. The individual regression lines are shown in figure below:

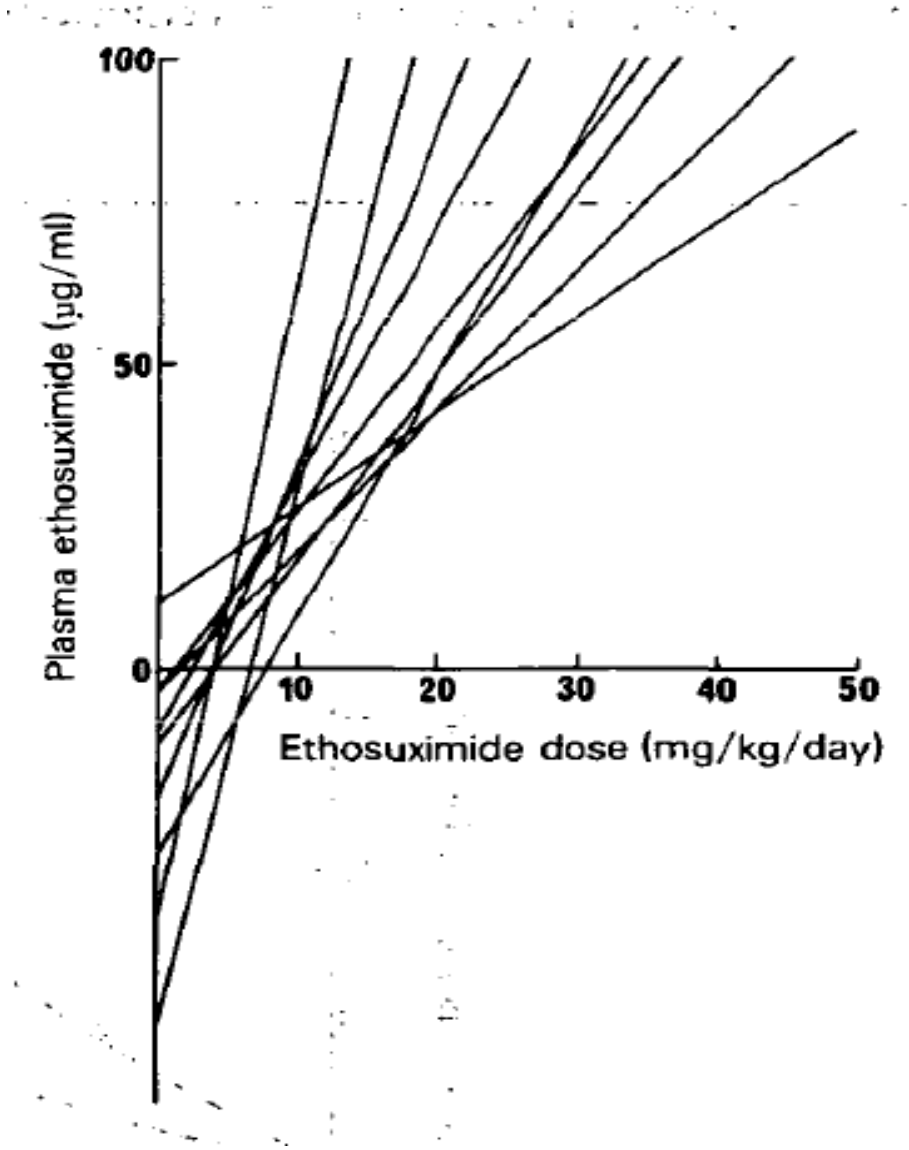



Figure 04: Individual least squares linear regressions for steady-state plasma ethosuximide level on drug dose in 9 subjects who had ethosuximide levels measured when taking 2 or more different ethosuximide doses. The tendency for the back extrapolated regression lines to have negative intercepts on the y axis is shown.

Eight of the 9 lines had negative intercepts on the y axis. This distribution of intercepts is Unlikely to be due to chance. Since in reality all regression lines must pass through the origin, the present findings suggest that the true shape of the regressions for plasma level on drug dose in the individual is curved, and that the shape conforms.to those shown in figure 03.

[redacted]

*2.5.3.3.1 Absorption*

Ethosuximide is practically completely absorbed after oral administration. Cmax values of 18 - 24 µg/ml were measured after the intake of 1 gm ethosuximide in three test persons after 1-4 hours. In adults under long-term treatment at a dose of ca. 15 mg/kg body weight a plasma concentration of about 50 µg/ ml was measured. At an oral dose of 1 mg/kg per day a plasma concentration of 2-3 µg/ml is to be expected. Steady state is expected to occur 8-10 days after start of treatment. Despite significant interindividual variation of plasma concentrations at the same oral dose, dose-linear dependence of plasma concentration was established. [redacted]

Ethosuximide is well absorbed by the gastrointestinal tract. Cmax is attained within 3 to 7 hours, and plasma concentrations do not start to decline until after the seventh hour. [redacted]
([redacted])

Absorption of ethosuximide was rapid, uniform, and proportional to dose and that there were no significant differences between the two dosage schedules (500 mg and 700 mg). [redacted]

**Table 01: Mean steady-state plasma levels of ethosuximide (mcg/ml)**

[redacted]

The total concentration of ethosuximide varied between 80 and 770 µmol/L in plasma samples obtained from 33 patients on long-term treatment with the racemic drug. The ratios between the two enantiomers measured by chiral gas chromatography in the same samples were close to unity (mean ± SD = 1.06 ± 0.14; range = 0.76-1.39). [redacted]

***2.5.3.3.2 Distribution***

Ethosuximide is not bound to plasma proteins. The drug is present in liquor and saliva in the same concentration as in plasma. The apparent volume of distribution is specified to be approximately 0.7 l/kg body weight. [redacted]

In adults, ethosuximide has been found to be only minimally bound to plasma protein; as a consequence, the plasma/CSF and plasma/saliva ratios approach unity. Assuming complete absorption, ethosuximide V/F is calculated as 0.7 L/kg. [redacted]

Ethosuximide passes the placenta barrier, and its plasma levels in neonates are similar to those in the mother. In report involving 10 epileptic mothers treated with ethosuximide and their newborns, the ratios of the fetal/maternal serum levels and milk/maternal serum levels were 0.97 ± 0.02 and 0.86 ± 0.08, respectively. [redacted]

Ethosuximide passes into breast milk; the ratio of the ethosuximide concentration of breast milk vs. plasma is specified to be 0.94 ± 0.06. [redacted]

***2.5.3.3.3 Metabolism***

Ethosuximide is extensively metabolized in the liver by oxidation. Several metabolites are produced, in particular the two diastereomeres of 2-(1-hydroxyethyl)-2-methyl succinimide and of 2-ethyl-2-methyl-3-hydroxysuccinimide. The metabolites are probably inactive. [redacted]

The metabolic pathways and the metabolites of ethosuximide are presented in figure 05 below. [redacted]

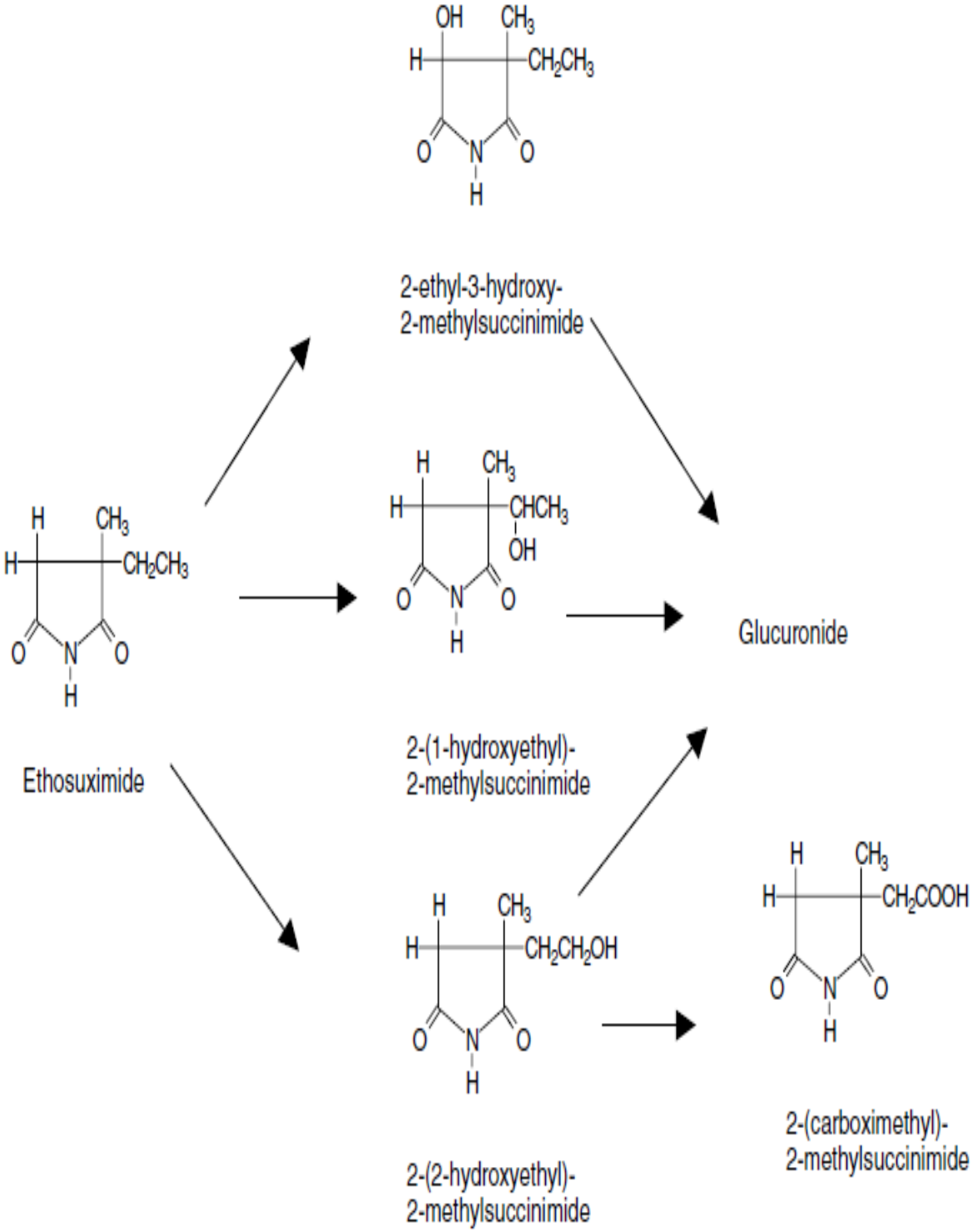



Figure 05: Metabolic Pathways and the Metabolites of Ethosuximide

Approximately 80% of ethosuximide undergoes hepatic metabolism, which is mediated primarily by cytochrome P450 isoenzymes, with a major contribution from CYP3A and, to a lesser extent, from CYP2E and CYP2C/B. The remainder, around 20% of an administered dose of ethosuximide, is excreted unchanged in the urine. The hydroxyethyl derivative known as the major metabolite of ethosuximide is inactive and is excreted as glucuronide in the urine. [redacted]

The human urinary metabolites of ethosuximide have been studied using chiral gas chromatography and gas chromatography/ mass spectrometry. The metabolites identified were unchanged ethosuximide enantiomers, all four stereoisomers of 2-(1-hydroxyethyl)-2-methylsuccinimide (II), and the four stereoisomers of 2-ethyl-3-hydroxy-2-methylsuccinimide (III). [redacted]

[redacted] investigated the urinary metabolites of a human subject who had received repeated doses of ethosuximide. The urine samples were firstly treated with β-glucuronidase. The samples were then passed on to an ion-exchange column and eluted with methanol. The methanol was evaporated and the residue silylated with bis-trimethylsilylacetamide. Samples indicated the presence of unchanged ethosuximide, the two isomers of 2-(1-bydroxyethyl)-2-methylsuccinimides (II) and a further metabolite that was originally identified as 2-acetyl-2-methylsuccinimide (III). [redacted]

[redacted] investigated the urinary metabolites of ethosuximide from several sources including volunteers receiving a single oral dose of ethosuximide and a 24-year-old female who had been receiving a 1 g1day dose of ethosuximide for 7 years. 4 major peaks were identified; unchanged ethosuximide, the isomers of 2(l-hydroxyethyl)-2-methyl succinimide (II) and 2ethyl-3-hydroxy-2-methyl succinimide (IV). [redacted]

[redacted] studied the urinary metabolites of ethosuximide in samples obtained from a 15-year-old boy who had been treated with 500 mg/day ethosuximide for 5 years. Metabolities identified were unchanged ethosuximide (I) and the isomers of 2-(I-hydroxyethyl)-2-methyl succinimide (II). In addition, author recorded the presence of two peaks that gave identical mass spectra: these were identified as diastereoisomers of the previously reported 2-ethyl-3-hydroxy-

2-methylsuccinimide (IV). Author also identified a previously unreported metabolite 2<arboxymethyl-2-methylsuccinimide (VI). [redacted]

***2.5.3.3.4 Elimination***

Between 10% and 20% of ethosuximide only is excreted unchanged in the urine. The main metabolites of ethosuximide, the two diastereomeres of 2-(1-hydroxyethyl)-2-methyl succinimide and of 2-ethyl-2-methyl-3-hydroxysuccinimide are to some extent conjugated and excreted renally as glucuronide. After a single oral dose of 13.1 - 18.0 mg ethosuximide/kg body weight given to 12 male test persons, plasma half-lives of 38.3-66.6 hours were measured. [redacted]

Ethosuximide is eliminated slowly from the body, and its half-life is therefore long. Individual values for half-life range from 25 to 42 hours after a single dose and from 14 to 78 hours at steady-state. No significant differences between half-life during the first and eighth weeks of treatment were found in the only published within-patient study. No differences in ethosuximide half-life have been seen in relation to plasma concentrations, dose/kg or formulation (syrup or capsules). [redacted]

There also were no significant differences in the elimination half-lives, with the mean being 53.9 hr for the single daily dose regimen and 52.6 hr for the divided daily dose group. [redacted]

***2.5.3.3.5 Pharmacokinetics in Special Populations***

***Pharmacokinetics in Renal Impairment***

Clearance of ethosuximide by hemodialysis was studied in four patients with chronic renal disease supported by hemodialyses who were given ethosuximide 500 mg four hours before dialysis. Samples of arterial and venous blood and dialysate were collected before and during the four-hour dialysis procedure. The extraction efficiency for the dialysis systems used in this study ranged from 61.1 to 100%, and dialysis clearance was from 122.3 to 156.3 ml/min. Recovery of ethosuximide from the dialysate was 38.8 to 52.4% of the administered dose. Hemodialysis reduced the elimination half-life of ethosuximide from a presumable value of 55 hours to an average of 3.5 hours. The authors concluded that ethosuximide is dialyzable. Hemodialysis patients concurrently receiving ethosuximide may require a supplemental dose or an altered ethosuximide dosing schedule. Because hemodialysis quickly clears ethosuximide, it may be useful in treating ethosuximide overdosage. [redacted]

***Pharmacokinetics in Paediatric Population***

After a single dose of 500 mg ethosuximide (capsules) given to 5 children, plasma half-lives of 25.7-35.9 hours were measured, with oral solution the plasma half-lives were 24.8-41.7 hours. [redacted]

In a study in children (7-8.5 years, 12.9-24.4 kg body weights) Cmax values of 28.0-50.9 μg/ml were measured 3-7 hours after the children had taken a single dose of 500 mg ethosuximide. Long-term treatment of children at 20 mg/kg body weight produces a plasma concentration of approximately 50 μg/ ml. In children an oral daily dose of 1 mg/kg produces a plasma concentration of 1-2 μg/ml. Therefore, younger children require a slightly higher dose than older children. [redacted]

***Pharmacokinetics in Pregnant Patient***

Pharmacokinetics study was conducted to observe the dose versus serum concentration relationship and the distribution of ethosuximide during pregnancy and lactation in an epileptic mother. In addition, the disappearance of transplacentally acquired ethosuximide from the serum of the newborn infant was studied. After delivery, maternal serum ethosuximide concentration appeared to increase at a constant ethosuximide dose. Levels in the range of 40 to 50 pg/ ml prior to delivery increased to the range of 60 to 75 pg/ml after delivery. Finally, the ratio of milk to serum ethosuximide concentration was found to be 0.94 ± 0.06. The half-life of elimination of transplacentally acquired ethosuximide in this neonate was 41.3 hr. The serum concentration of ethosuximide in cord blood obtained by milking the umbilical cord at birth was 61.9 pg/ ml. [redacted]

***Pharmacokinetics in Different Age***

The relations between plasma ethosuximide level and drug dose in patients under [redacted] years of age **(**14 subjects) and in patients over [redacted] years of age (20 subjects) were compared to see if the relations differed between pre- and post-pubertal subjects. Analysis of covariance showed no statistically significant differences in the slopes or elevations of the linear regressions for these 2 age groups (figure plotted below). [redacted]

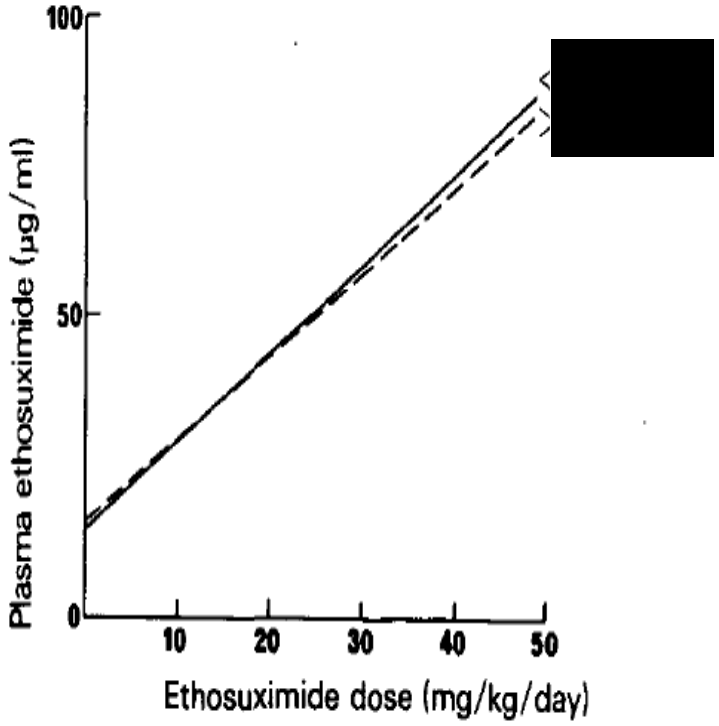



Figure 06: Linear regressions for steady-state plasma ethosuximide level on drug dose in persons under [redacted] years and in persons over [redacted] years

The relationship between oral dose and plasma concentration of ethosuximide was evaluated retrospectively in 198 epileptic patients aged 2.5 to 34 years. Age appears to be a major factor in determining the ethosuximide plasma level/dose ratio. Children younger than [redacted] years had mean level/dose ratios significantly lower than adolescents [redacted] years of age) and adults ([redacted] years of age). Associated antiepileptic therapy reduced the ethosuximide lethal/ dose ratio; mean ethosuximide lethal/dose ratios were significantly lower in patient's also taking primidone or valproic acid. The correlation between the dose of ethosuximide administered and the plasma concentration was significant in the 3 age groups considered, but the wide scattering of individual plasma concentrations makes it impossible to predict what plasma concentration of ethosuximide will be obtained after a given dose. For this reason, routine monitoring of ethosuximide plasma concentrations still appears to be necessary, especially in children and patients on polytherapy. [redacted]

***Pharmacokinetics in Different Sex***

The linear regressions for plasma ethosuximide level on drug dose were compared in males and females by means of analysis of covariance (figure below). The regressions differed in slope, levels increasing more steeply relative to dose in females. [redacted]

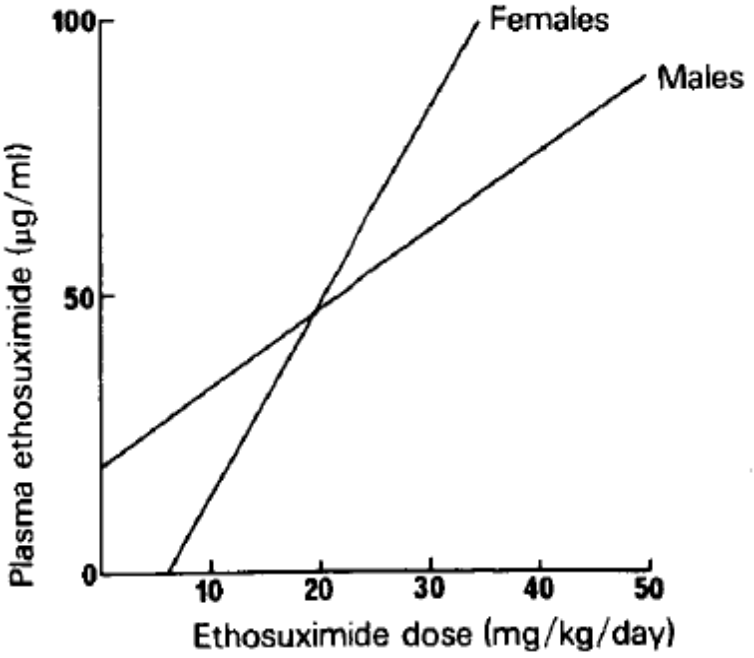



Figure 07: Linear regressions for steady-state plasma ethosuximide level on drug dose in males and females.

### *2.5.3.4 Drug Interactions*

#### *2.5.3.4.1 Pharmacokinetic Drug Interactions*

Effects of other medicinal products on ethosuximide

The concomitant administration of carbamazepine increases the plasma clearance of ethosuximide. Valproic acid may increase the plasma concentration of ethosuximide in most patients.

Effects of ethosuximide on other medicinal products

Ethosuximide normally does not change the plasma concentration of other anti-epileptics such as primidone, phenobarbital and phenytoin since ethosuximide is not an enzyme inductor. However, individual cases of elevated phenytoin concentration were reported when ethosuximide was administered concomitantly.

[redacted]

Interaction with enzyme inducing anticonvulsants:

[redacted] assessed the effect of enzyme inducing anticonvulsants on ethosuximide pharmacokinetics, plasma ethosuximide concentrations after a single oral dose (500 mg) of the drug were compared in 12 healthy control subjects and 10 epileptic patients receiving chronic therapy with phenobarbitone, phenytoin and/or carbamazepine. Compared with controls, epileptic patients showed markedly shorter ethosuximide half-lives (29.0 ± 7.8 vs 53.7 ± 14.3 h) and higher apparent oral clearance values (15.3 ± 3.8 vs 9.2 ± 1.9 ml kg−1 h−1). The apparent volume of distribution of ethosuximide was slighty lower in the patients than in controls (0.6 ± 0.1 vs 0.7 ± 0.1 l kg−1). These findings provide evidence that ethosuximide elimination is increased by enzyme inducing anticonvulsants, the effect probably being mediated by stimulation of cytochrome CYP3A activity. The enhancement of ethosuximide clearance in patients comedicated with enzyme inducing anticonvulsants is likely to be clinically relevant. [redacted]

Interaction with Valproic Acid:

Concurrent administration of valproic acid with ethosuximide was reported either to increase or decrease plasma levels of ethosuximide. ([redacted]

The addition of valproic acid to ethosuximide in treatment to prevent seizures caused increased serum concentration of ethosuximide in four of five patients observed. Ethosuximide levels increased from 73 to 112 µg/mL (53% higher), with concomitant toxicity. Both were reversed by reduction of the ethosuximide dose from 27.4 to 20.4 mg/kg. Serum concentrations of these two drugs should be monitored closely when they are given together. [redacted]

Ethosuximide kinetics were determined in six normal healthy adults after a single dose (phase 1) and at steady-state (phase 2). After the completion of phase 2, valproic acid was added to the ethosuximide regimen (phase 3) to assess the possibility of drug interaction. Between phases 1 and 2 total clearance fell from 13.1 to 11.1 ml/hr/kg and non-renal clearance fell from 10.1 to 8.3 ml/hr/kg. When valproic acid was added (phase 3) there was no further change in total or non-renal clearance (11.2 and 8.3 ml/hr/kg). To assess the possibility of nonlinear ethosuximide kinetics a review was conducted of patients who received ethosuximide as sole therapy for absence seizures. Of 106 patients, 10 met the required criterion that defined steady state. Data from 07 of 10 patients showed evidence of a non-linear relationship when steady state ethosuximide concentrations were plotted against dose. [redacted]

Influence of ethosuximide on valproic acid serum concentrations was studied in children with epilepsy. Serum levels of valproic acid were higher in monotherapy than in combination with ethosuximide (120 µg/ mL vs 87 µg/ mL). The difference was statistically significant. After stopping ethosuximide the serum concentrations of valproic acid rose about 36.7%; when combined with ethosuximide they fell about 28.3%. Neither the age of the patients nor the serum concentrations of ethosuximide influenced significantly the changes of valproic acid serum levels in either group. The interaction of ethosuximide and valproic acid ought to be considered in a combination therapy of these drugs. The results of this study show a clear-cut influence of ethosuximide on the serum levels of valproic acid. In ethosuximide and valproic acid combination therapy, serum concentrations of valproic acid were decreased compared with the serum concentrations of valproic acid in monotherapy intra-individually. [redacted]

A pharmacokinetic study was designed to investigate the possible interaction between valproic acid and ethosuximide in humans. Six drug-free healthy volunteers, four men and two women, received a single oral dose of 500 mg ethosuximide before and during a treatment with valproic acid at 800- to 1,600-mg daily doses. The second ethosuximide dose was given 9 days after valproic acid administration was started. In this latter condition, a significant increase in ethosuximide serum half-life, from 44 to 54 h on average, and a significant decrease in total body clearance, from 11.2 to 9.5 ml/min on average, was observed. Other pharmacokinetic parameters were unchanged and showed values similar to those reported in the literature. Serum valproic acid levels ranged between 66.8 and 95 µg/ml. Two subjects showed no evidence of

interaction. Although a great interindividual variability in the occurrence of valproic acid - ethosuximide interaction can be observed. The present study indicates that valproic acid is able to inhibit the metabolism of ethosuximide. [redacted]

Interaction with Methylphenbbatbitone:

Concurrent administration of Methylphenbbatbitone tended to raise plasma ethosuximide levels relative to ethosuximide dose. [redacted]

Interaction with Rifampicin:

In healthy volunteers, rifampicin was shown to increase ethosuximide clearance. [redacted]

Interaction with Carbamazepine:

Carbamazepine and ethosuximide are used together to treat epileptic mixed-seizure patterns. Since carbamazepine has been shown to induce drug-metabolizing enzyme(s) in the liver, it follows that carbamazepine may alter ethosuximide disposition. Six normal subjects took one 250-mg ethosuximide capsule twice each day for 55 consecutive doses (study days 1 to 28) and one 200-mg carbamazepine tablet each evening from study days 11 to 27. Plasma samples were collected on study days 10, 17, 21, and 28. Mean steady-state concentrations of ethosuximide declined by 17% from a preinduction (study day 10) level of 32.2 ± 5.6 µg/ ml to a post-induction level of 26.8 ± 5.2 µg/ ml on study day 28. Ethosuximide clearance increased between study days 10 and 28 from 0.664 ± 0.120 to 0.800 ± 0.0154 1/ hr. The time course of induction was analyzed using a kinetic induction theory. Ethosuximide was lowered from 53.7 ± 11.5 hr (before induction) to 44.6 ± 10.7 hr (after induction); the difference between some subjects was large. These data show that ethosuximide disposition is altered by carbamazepine. [redacted]

Interaction with Lamotrigine:

Pharmacokinetic interaction between lamotrigine and ethosuximide was evaluated in epileptic children. No clinically important changes in the plasma levels of ethosuximide were observed in the follow-up period of 2 -12 months. Hence, no dose adjustment is necessary. [redacted]

***2.5.3.4.2 Pharmacodynamic Drug Interactions***

The simultaneous use of medicinal products affecting the central nervous system, alcohol or convulsion-inducing substances and ethosuximide should be avoided.

[redacted]

Interaction with Contraceptives:

A drug interaction study of ethosuximide with contraceptive hormones revealed that ethosuximide does not interact significantly with oral contraceptives. [redacted]

Suximides do not have enzyme-inducing properties so it is unlikely that there will be significant drug interactions with the combined oral contraceptive pill. [redacted]

***2.5.3.5 Pharmacokinetic – Pharmacodynamic Relationship***

The therapeutic plasma concentration of ethosuximide is 40-100 μg/ml. Plasma concentrations of more than 150 μg/ ml may have toxic effects. [redacted]

A study was conducted in 9 children with petit mal epilepsy to compare the plasma levels of ethosuximide after divided daily administration with those after single daily administration. The children received their previously established dose in divided doses for 4 week, in single morning doses for 4 week, and again in divided doses for 4 week. None of the children suffered petit mal seizures during the study. Three had grand mal seizures but the frequency did not differ between the dosage regimens. Plasma levels during the single-dose period peaked more rapidly and fell more quickly than during the other periods, but mean levels remained in the therapeutic range. The mean half-life of the drug in these children was 29 hr. For reasons not understood, plasma levels generally were lower in the second divided dose period than in the other two periods. No adverse experiences were reported during the study. The data indicate that ethosuximide is clinically effective when given in a single daily dose. This regimen offers advantages in convenience and possibly in patient compliance. [redacted]

### *2.5.3.6 Posology*

Adults, elderly patients and children over 6 years of age: The treatment is started at a daily dose of 500 mg.

Depending on the patient's tolerance, the dose is increased every five to seven days in increments of max. 250 mg until the seizures are controlled by a daily dose of 1000 - 1500 mg. In an individual case, a daily dose of 2000 mg, taken in several single doses, may be required.

The therapeutic plasma level of ethosuximide is normally between 40 and 100 µg/ml. However, the dose depends on the patient's clinical response. The half-life of ethosuximide in plasma is more than 24 hours so that the daily dose can be taken as a single dose provided the medicinal product is well tolerated. Higher daily doses should be taken in 2 or 3 single doses, however.

The probability of dose-dependent undesirable effects can be reduced by careful dosing (small initial dose at the start of treatment, gradual increase of dose) and by taking the medicinal product during or after meals.

Anti-epileptic therapies are principally long-term therapies. A specialist (neurologist, neuropaediatrician) should decide about the start, duration and discontinuation of ethosuximide on an individual basis.

In general, reduction of the dose and discontinuation of the medicinal product should not be considered before the patient has been free from fits for 2-3 years.

The medicinal product must be discontinued by reducing the dose gradually over a period of one to two years. Children may be allowed to outgrow the dose per kg body weight instead of adjusting the dose according to their age; however, it must be ensured that the EEC findings do not deteriorate.

***Special populations***

***Haemodialysis patients***

Ethosuximide is dialysable. Haemodialysis patients therefore require a supplementary dose or a modified dose regimen. During a dialysis period of four hours, 39% to 52% of the dose taken is removed.

***Children***

Children under 2 years:

The treatment is started at a daily dose of 125 mg (2.5 ml). The dose is increased gradually in small increments every few days until the fits are controlled.

Children between 2 and 6 years:

The treatment is started at a daily dose of 250 mg (5 ml). The dose is increased gradually in small increments every few days until the fits are controlled.

The optimum daily dose for most children is 20 mg/kg. The maximum daily dose is 1000 mg.

**Method of administration**

Ethosuximide is for oral use.

The solution can be taken during or after meals.

[redacted]

## 2.5.4 OVERVIEW OF EFFICACY

Ethosuximide, a succinimide-based molecule, has a narrow therapeutic profile in the treatment of epilepsy. The agent is the drug of choice in the monotherapy or polytherapy of children with generalized absence (petit mal) epilepsy. Ethosuximide and valproate were demonstrated to be equally effective in reducing generalized spike-and-wave discharges in previously untreated patients with absence seizures in a crossover study, and to have equal efficacy in achieving complete remission of absence seizures. Moreover, the combination therapy with ethosuximide and valproate was found to be superior to the monotherapy with either valproate or ethosuximide in terms of efficacy in patients with refractory absence seizures in a five-patient open-label study. Patients with atypical absence epilepsy who exhibit other types of seizures including tonic–clonic seizures and drop attacks may respond to ethosuximide combined with other antiepileptic agents. Even though (due to poor design of studies) there is no conclusive evidence for a high degree of efficacy of any epileptic drug in the initial monotherapy of childhood and juvenile absence epilepsy, ethosuximide is considered to have similar efficacy/effectiveness as valproate in this condition. [redacted]

Ethosuximide, a-ethyl a-methyl succinimide, is one of a family of succinimides that were developed in response to the need for a safe and effective drug for the treatment of absence seizures. An initial observational study conducted over a mean of 37 weeks of treatment found that 42% of 109 patients had complete seizure control, with an additional 24% having had 80–99% reduction in seizures. In patients characterized as pure absence epilepsy, 61% had complete control. [redacted]

An observational study of 100 patients, 80 of whom were reported to have ‘‘typical petit mal,’’ had a mean of 10 months of treatment with ethosuximide. Although 73% were improved, 48% had complete seizure control. ([redacted]

Early observational studies depended upon seizure counts recorded by an observer. With the addition of video recording and seizure counting by trained observers, ethosuximide treatment was associated with complete control of absence seizures in 49% of patients, with 50% - 100% control in 95%. [redacted]

Thirty-seven patients with previously untreated absence seizures were treated with ethosuximide. Seizures were completely controlled in 7 patients (19%); 90 to 100 percent control was achieved in 18 patients (49%) and 50 to 100 percent control in 35 (95%). Plasma ethosuximide concentration increased with dose, but variability in the plasma concentration produced by a given ethosuximide dose made it impossible to predict a patient’s plasma concentration from the dose. The therapeutic range of plasma ethosuximide concentration was 40 to 100 pg per

milliliter. Patients with evidence of structural central nervous system abnormalities responded as well or better to the drug as patients without such evidence. Ethosuximide did not impair psychometric performance, but rather resulted in improved performance in 17 cases. ([redacted]

A Cochrane review was conducted to report the evidence for the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures, when compared with placebo or each other. Randomised parallel group monotherapy or add-on trials which include a comparison of ethosuximide; sodium valproate; lamotrigine; or placebo in children or adolescents with absence seizures were included. Eight small trials were found. Six of them were of poor methodological quality and seven recruited less than 50 participants. There are no placebo-controlled trials for ethosuximide or valproate, and hence, no evidence from randomised controlled trials to support a specific effect on absence seizures for either of these two drugs. Due to the differing methodologies used in the trials comparing ethosuximide, lamotrigine and valproate, we thought it inappropriate to undertake a meta-analysis. One large randomised, parallel double-blind controlled trial comparing ethosuximide, lamotrigine and sodium valproate in children with newly diagnosed childhood absence epilepsy found that at 12 months, the freedom-from-failure rates for ethosuximide and valproic acid were similar and were higher than the rate for lamotrigine. The frequency of treatment failures due to lack of seizure control and intolerable adverse events was significantly different among the treatment groups, with the largest proportion of lack of seizure control in the lamotrigine cohort, and the largest proportion of adverse events in the valproic acid group. Overall, this large study demonstrates the superior effectiveness of ethosuximide and valproic acid compared to lamotrigine as initial monotherapy aimed to control seizures without intolerable adverse effects in children with childhood absence epilepsy. Authors concluded that with regards to both efficacy and tolerability, ethosuximide represents the optimal initial empirical monotherapy for children and adolescents with absence seizures. [redacted]

***Children***

The 2010 Childhood Absence Epilepsy study provided class I evidence for the use of ethosuximide as the optimal initial treatment for CAE. This double blind, randomized, controlled trial enrolled 453 children between the ages of 4 and 10 years with newly diagnosed and untreated CAE, who had absence seizures only and no history of generalized tonic–clonic seizures. Participants were randomly assigned to treatment with ethosuximide ($n$ = 156), valproic acid ($n$ = 148), or lamotrigine ($n$ = 149). The primary outcome measure was freedom from failure, defined as the absence of clinically apparent seizures (based on parent report) or electrographic seizures at 16–20 weeks of treatment, and the absence of treatment-limiting adverse effects. Seven participants were ineligible after randomization, and the analysis cohort

included 446 children. The freedom-from-failure rates for ethosuximide and valproic acid were similar and were higher than the freedom-from failure rate for lamotrigine (when compared to both ethosuximide and valproic acid). The study concluded that ethosuximide and valproic acid are more effective than lamotrigine for initial monotherapy of CAE, and of these two, ethosuximide is the most optimal treatment. [redacted]

Of 175 patients treated with ethosuximide, 58 were naive to treatment and 133 were reported to have ‘‘typical petit mal,’’ some with ‘‘grand mal’’ as well. Of the children in this study, 65% were almost completely controlled. [redacted]

A study was performed to evaluate the long-term efficacy of ethosuximide, valproic acid and lamotrigine as initial monotherapies for patients with newly diagnosed childhood absence epilepsy. Investigators retrospectively reviewed the medical records of 128 patients (45 boys and 83 girls) diagnosed with childhood absence epilepsy at the Seoul National University Hospital. Seizure-free rate and the retention rate were observed during 2 years of treatment. Follow-up electroencephalography (EEG) was performed. The seizure-free rate of ethosuximide (84%) was significantly higher than that of valproic acid (62%) and lamotrigine (53%) at 3 months. The seizure-free rate of ethosuximide (90%) was significantly higher than that of lamotrigine (63%) at 6 months. After 9 months, there was no significant difference in seizure-free rate among the three groups. There were no significant differences among the three groups in terms of normalization of EEG at 12 months (ethosuximide: 77%; valproic acid: 83%; and lamotrigine: 64%) and retention rate throughout the whole treatment period. Study suggests that ethosuximide, valproic acid and lamotrigine are equally effective in the long-term treatment of newly diagnosed CAE patients. However, the onset of efficacy was faster for ethosuximide compared with valproic acid lamotrigine. [redacted]

Eleven children with typical absence seizures were studied clinically and by repeated 24-h EEGs with portable cassette tape recorder before and during anticonvulsant treatment. The history, the observation of seizures and the amount of spike-and-wave activity (episodes >3 sec) were studied. The EEG revealed spike-and-wave episodes, considered as seizures, in a higher frequency than the number of absences reported by the parents. Twenty-four hour EEG recording was however not superior to long term observation by relatives in establishing freedom from absences. The drug primary used was ethosuximide. All children reported a reduced frequency of absences on ethosuximide therapy. Eight of eleven children responded completely on this drug, i.e. no absences observed and EEG was normalized. Of two children in whom the therapy was changed to sodium valproate, one responded completely and one partly. Tonic-clonic seizures occurred in 3/11 children. The therapeutic results with ethosuximide reported a complete remission in 8 and partial in 3 cases. [redacted]

[redacted] used ethosuximide as an adjunctive anticonvulsant drug in 19 children with multiple seizure types in whom the primary and most troubling seizure was falling to the ground. All patients were having multiple, daily falls, intractable to phenobarbital, valproic acid, and clonazepam. Seizures were characterized and quantitated by video-electroencephalographic telemetry. Twelve children became completely free of epileptic falls on ethosuximide. Four children showed a 50%-75% decrease in the number of falls while 3 showed no change in frequency of falls. All children had an abnormal electroencephalogram (EEG) prior to starting ethosuximide with generalized bursts of spike and wave in a frequency range of 1-4 cycles per second (cps). The only EEG abnormality common to those patients who became free of epileptic falls with ethosuximide treatment was a generalized, synchronous 4 cps discharge. Results suggests that ethosuximide may be a valuable adjunctive treatment for epileptic falling spells that occur in the context of multiple seizure types. ([redacted]

[redacted] determined optimal second monotherapy for children with childhood absence epilepsy (CAE) experiencing initial treatment failure. Children with CAE experiencing treatment failure during the double-blind phase of a randomized controlled trial comparing ethosuximide, valproic acid, and lamotrigine were randomized to open-label second monotherapy with one of the 2 other study therapies. Primary study outcome was freedom from failure proportion at week 16–20 and month 12 visits after randomization. Secondary study outcome was percentage of participants experiencing attentional dysfunction at these visits. A total of 208 children were enrolled, randomized, and received second therapy. At both week 16–20 visit and month 12 visit, ethosuximide's (63%, 57%) and valproic acid's (65%, 49%) freedom from failure proportions were similar to each other and higher than lamotrigine (45%, 36%). At both the time points, ethosuximide and valproic acid had superior seizure control compared to lamotrigine. At both the week 16–20 and month 12 visits, attentional dysfunction was numerically more common with valproic acid than with ethosuximide or lamotrigine. For each medication, second monotherapy freedom from failure proportions demonstrated non-inferiority to initial monotherapy freedom from failure proportions. Study results conclude that, as second monotherapy, ethosuximide and valproic acid, demonstrated higher freedom from failure proportions and greater efficacy than lamotrigine; valproic acid was associated with more attentional dysfunction. Ethosuximide is the optimal second monotherapy for children with CAE not responding to initial therapy with other medications. [redacted]

A study was conducted to evaluate the effectiveness of ethosuximide in the treatment of epileptic negative myoclonus, a motor disorder that can occur in childhood partial epilepsy. Investigators introduced ethosuximide in 09 patients with partial epilepsy of varying etiology (idiopathic, cryptogenic, symptomatic) who presented with epileptic negative myoclonus. The drug was added to the patients' preexisting antiepileptic drugs, which were maintained unchanged for the following 6 months. Epileptic negative myoclonus disappeared in all patients 15 to 30 days after

ethosuximide was started. The clinical response was not influenced by the patients' preexisting treatment or by the etiology of the epilepsy. No side effects were observed, and none of the patients presented a recurrence of epileptic negative myoclonus during follow-up. Furthermore, in five patients reported disappearance of partial seizures; in the remaining patients seizures were reduced by more than 75%. Electroencephalograms showed a decrement or disappearance of focal paroxysmal abnormalities. Study results suggest that ethosuximide is effective in the treatment of epileptic negative myoclonus and that it should be considered as a first-choice drug in the treatment of this motor disorder. [redacted]

## 2.5.5 OVERVIEW OF SAFETY

### *2.5.5.1 Undesirable Effects, Safety and Tolerability*

The frequency of possible undesirable effects is defined using the following convention:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (> 1/1,000 to < /100)
Rare (> 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

Within the therapeutic dose range undesirable effects are common and have been observed in about 1/6 of patients. These are mainly nausea, vomiting, singultus and abdominal pain.

Blood and lymphatic system disorders

Rare: Leucopenia, thrombocytopenia, agranulocytosis, eosinophilia
Not known: In individual cases aplastic anaemia and pancytopenia have been observed.

Metabolism and nutrition disorders

Uncommon: Loss of weight, loss of appetite

Psychiatric disorders

Uncommon: Withdrawal, anxiety, sleep disturbances
Rare: Paranoid and hallucinatory phenomena developing over days and weeks.

Nervous system disorders

Uncommon: Severe headache, ataxia, lethargy
Not known: A few individual cases of dyskinesia have been reported for the period of the first 12 hours after start of the treatment; it disappeared soon after discontinuation of ethosuximide or the administration of diphenhydramine.

Respiratory, thoracic and mediastinal disorders

Common to very common: Singultus
Gastrointestinal disorders

Common to very common: Nausea, vomiting, abdominal pain
Uncommon: Diarrhoea, constipation

Skin and subcutaneous tissue disorders

Rare: Lupus erythematodes of varying extent
Not known: Allergic skin reactions such as exanthema, but also the severe generalised form of Stevens- Johnson syndrome may occur.

If undesirable effects occur which are independent of the dose taken and reversible, the medicinal product should be discontinued. They may reappear when the medicinal product is taken again.

Long-term treatment may affect the patient's performance, e.g. the performance in school of children and adolescents.

[redacted]

***2.5.5.1.1 Overview of Clinical Safety Data***

Commonly observed dose-dependent side effects of ethosuximide in patients are related to the gastrointestinal tract or central nervous system. Nausea, abdominal discomfort, vomiting, diarrhea, and anorexia are common at the onset of ethosuximide therapy. Central nervous system effects include drowsiness, dizziness, hiccups, fatigue, insomnia, tiredness, headache, and psychotic behaviors. Ethosuximide has been also associated with a wide variety of idiosyncratic reactions, including allergic dermatitis, rash, Stevens-Johnson syndrome, systemic lupus erythematosus, lupus-like syndrome, serum sickness reaction, agranulocytosis, and aplastic anemia. Hematopoietic adverse effects include leukopenia, agranulocytosis, eosinophilia, and pancytopenia. Ethosuximide-induced agranulocytosis was observed in a 16-month-old male infant with Down syndrome. [redacted]

Ethosuximide causes some side effects that tend to be gastrointestinal in nature, but adverse effects related to the central nervous system including dizziness, sedation, and behavioral changes have been reported as well. Pruritic rashes and blistering exanthema have occurred also, including the Stevens-Johnson syndrome. Other serious idiosyncratic effects such as aplastic anemia have occurred. Adverse effects in a small number of patients were reported in an initial

observational study (n=109) conducted over a mean of 37 weeks of treatment included drowsiness, dizziness, nausea, and gastric distress. In observational study of 100 patients, 31% of patients had either side effects or toxic effects, with abdominal pain, nausea, sedation, and headache being most common. Six patients had rash. [redacted]

Although gastrointestinal side effects are by far the most commonly reported side effects with Ethosuximide, they are rarely the sole reason for drug discontinuation. These benign and fully reversible side effects include abdominal discomfort, vomiting, diarrhea, and hiccups. Measures that may improve gastrointestinal discomfort include taking the medication with food and switching from liquid to the capsule form. The neurologic side effects and adverse reactions of Ethosuximide can include headaches, sedation, fatigue, insomnia, ataxia, or extrapyramidal reactions. Rarely, clinically apparent behavioral disturbances may occur, including nervousness, irritability, depression, hallucinations, and even psychosis. Blood dyscrasias occur rarely with Ethosuximide; clinical alertness to possible signs and symptoms is a more useful and more cost effective way of recognizing these rare adverse drug reactions than routine monitoring of blood counts. Ethosuximide induced lupus is a rare adverse drug reaction, appearing in the medical literature mostly as single case reports. Symptoms typically resolve with cessation of ethosuximide, but recovery may be prolonged. Other idiosyncratic adverse drug reactions include allergic rashes, which typically resolve with medication withdrawal. [redacted]

A double-blind, randomized controlled clinical trial compared the tolerability of ethosuximide, valproic acid and lamotrigine in children with newly diagnosed childhood absence epilepsy. Overall, the most common of these 20 different adverse events were fatigue and headache. Stomach upset, nausea, and vomiting occurred more frequently (defined as 5% greater occurrence in one treatment group compared to either of the other treatment groups) in the ethosuximide group. Weight increase, hyperactivity, attention problems, hostility, decreased concentration, personality change, and sleep problems were reported more frequently in the valproic acid group. No side effect occurred more frequently in the lamotrigine cohort compared to the other treatment cohorts. By the Month 12 visit, eight subjects (2%) had had serious adverse events that required hospitalization: four in the ethosuximide group and two each in the lamotrigine and valproic acid groups. Reasons for hospitalization included generalized tonic–clonic seizures in three subjects. The study concluded that ethosuximide is the most optimal treatment because it is associated with a lower risk of adverse effects on attention. [redacted]

Thirty-seven patients with previously untreated absence seizures were treated with ethosuximide. Seven types of side effects occurred 19 times in 13 of 39 (33%) patients. Nausea, the most common side effect, occurred in nine patients, with vomiting in one. The nausea usually

occurred during the first few days of ethosuximide administration. Two patients were withdrawn from ethosuximide early in the study because of several days of nausea on the standard dosage of 750 mg per day. One patient exhibited extreme irritability when started on ethosuximide and the drug was withdrawn for 1 week. The irritability lessened with continued ethosuximide administration, and psychometric test performance improved between the placebo week and the eighth treatment week. Leukopenia developed in one patient. Over the first 3 weeks of ethosuximide administration, her white blood cell count dropped from 6,100 per cubic millimeter to 2,600 per cubic millimeter. The percent neutrophils in her differential white cell count dropped from 55 to 19. At this point, the ethosuximide dosage was reduced from 750 to 250 mg per day. Over the next 6 weeks, her white blood cell count and differential returned to normal. [redacted]

Twenty subjects, in a double-blind, controlled, rising dose study, were given ethosuximide either once daily or 3 times daily. Hematopoietic and renal functions were checked twice during the screening period and weekly from day 1 to day 43. Subjects were observed closely for volunteered symptoms, which were all recorded. Volunteered symptoms, of which mild headache was the most frequent, were equivalent in both groups. Side effects were generally mild, medication being well tolerated throughout the trial. Two subjects in the group which was receiving ethosuximide as a single 500 mg A.M. dose were dropped, one complaining of nervousness, the other of epigastric distress. Another subject was dropped for administrative reasons. Periodic frequent laboratory determinations showed no deviations in the population that were not expected. Physical examination and other clinical findings were normal before, during, and after the trial. [redacted]

***2.5.5.1.2 Safety for Pregnancy and Lactation***

**Women of childbearing potential**

Women of childbearing potential should be advised by their doctor of the necessity of planning and monitoring a pregnancy before starting the treatment with ethosuximide. Patients should be advised to tell their doctor immediately if they have become pregnant during the treatment. [redacted]

**Pregnancy**

The treatment with ethosuximide should not be interrupted during pregnancy without the consent of a physician as the sudden discontinuation of the treatment or uncontrolled reduction of the dose may result in recurrence of epileptic seizures which may harm the pregnant woman and/or the unborn child. Ethosuximide crosses the placenta. Studies in animals have shown reproductive

toxicity. Specific congenital malformations have not been observed in children of mothers exposed to ethosuximide monotherapy during pregnancy. The risk of malformations during antiepileptic therapy is increased by a factor of 2 to 3 compared to the expected incidence of about 3% in the general population. Most common malformations reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapies are associated with a higher risk of congenital malformation so that monotherapy should be practiced during pregnancy whenever possible.

Patients should be informed of the increased risk of malformations and prenatal diagnostic measures should be offered.

The lowest effective dose ensuring seizure control must not be exceeded, particularly during the 20th and 40th day of pregnancy. The ethosuximide serum concentration of the pregnant woman must be regularly monitored.

Folic acid supplementation is recommended in patients planning to have a baby and during pregnancy. To prevent vitamin K1 deficiency and reduce the risk for haemorrhages in newborn infants, women should be given vitamin K1 during the last month of pregnancy.

[redacted]

Around 10 epileptic mothers treated with ethosuximide as well as their 13 newborns were evaluated. Two major malformations (bilateral clefting, hare-lip) were observed in two neonates whose mothers received ethosuximide / phenobarbital or ethosuximide / primidone comedication. The number of minor anomalies was higher in the ethosuximide group (6.2, n = 12) than in the pair-matched control group of infants born to non-epileptic mothers (2.1, n = 10). Neonatal behaviour complications occurred in seven infants, two of them were severely affected. ([redacted]

Veroniki et al compare the risk of congenital malformations and prenatal outcomes of AEDs in infants/children who were exposed to AEDs in utero through a systematic review and Bayesian random-effects network meta-analysis. Across all major congenital malformations, many AEDs were associated with higher risk compared to control. For major congenital malformations, ethosuximide, valproate, topiramate, phenobarbital, phenytoin, carbamazepine and 11 polytherapies were significantly more harmful than control, but lamotrigine and levetiracetam were not. [redacted]

**Lactation**

Ethosuximide is excreted into breast milk reaching concentrations up to 94% of the maternal serum concentrations. Sedation, poor suckling and irritability have been observed in individual breast-fed infants. Breast-feeding should be discontinued during treatment with ethosuximide. [redacted]

Ethosuximide is considered to be potentially dangerous during lactation and monitoring breastfed infant has been suggested. ([redacted]

***2.5.5.1.3 Safety in Paediatric Population***

Common adverse effects associated with ethosuximide include gastrointestinal disturbances, anorexia, weight loss, drowsiness, photophobia, headache, and behaviour and psychotic disturbances. Rare adverse effects include aplastic anaemia, serious skin reactions, and renal and hepatic impairment. [redacted]

In paediatric study involving 175 patients, side effects included gastrointestinal symptoms, headache, drowsiness, and dizziness. Rash was reported to be a transient problem in five patients and three had hematologic problems. ([redacted]

[redacted] determined incidence and early predictors of generalized tonic-clonic seizures (GTCs) in children with childhood absence epilepsy (CAE). Occurrence of GTCs was determined in 446 children with CAE who participated in a randomized clinical trial comparing ethosuximide, lamotrigine, and valproate as initial therapy for CAE. The cohort had been followed for a median of 7.0 years since enrollment and 12% (53) have experienced at least one GTC. The median time to develop GTCs from initial therapy was 4.7 years. The median age at first GTC was 13.1 years. Among patients initially assigned to ethosuximide, 94% (15/16) with GTCs experienced initial therapy failure. A similar but more modest effect was noted in those initially treated with valproate and not seen in those initially treated with lamotrigine. The occurrence of GTCs in a well-characterized cohort of children with CAE appears lower than previously reported. GTCs tend to occur late in the course of the disorder. Children initially treated with ethosuximide who are responders have a particularly low risk of developing subsequent GTCs. ([redacted]

A study was performed to evaluate the long-term tolerability of ethosuximide, valproic acid and lamotrigine as initial monotherapies for patients with newly diagnosed childhood absence epilepsy. Investigators retrospectively reviewed the medical records of 128 patients (45 boys and 83 girls) diagnosed with childhood absence epilepsy at the Seoul National University Hospital. Adverse events were identified in 31 patients (24%). There were no significant differences in adverse event rates among the treatment groups. The frequent or specific adverse events associated with AEDs were drowsiness and gastrointestinal complaints, such as nausea,

vomiting, and abdominal pain, for ethosuximide and valproic acid, alopecia for valproic acid, and rash for lamotrigine. The frequent causes of AED withdrawal because of the development of adverse events were gastrointestinal complaints for ethosuximide (5/48 patients, 10%), gastrointestinal complaints (3/59 patients, 5%) and alopecia (4/59 patients, 7%) for valproic acid and rash (1/21 patient, 5%) for lamotrigine. Seven patients (15%) in the ethosuximide group, 13 patients (22%) in the valproic acid group, and six patients (29%) in the lamotrigine group discontinued the treatment because of poor seizure control. [redacted]

### *2.5.5.2 Overdosage*

Whenever evaluating an overdose, potential multiple intoxication should principally not be excluded e.g. several medicinal products have been taken with a suicidal intent. The symptoms of overdose are potentiated under the influence of alcohol and other CNS depressants.

Symptoms of intoxication

Ethosuximide has a low toxicity. The symptoms listed as undesirable effects such as tiredness, lethargy, depression and agitation, also irritability, are more frequent or severe in the case of intoxication.

If intoxication is suspected, it is recommended to determine the plasma concentration of the antiepileptics.

Treatment of intoxication

Significant overdoses require initial gastric lavage and the administration of activated charcoal as well as monitoring of the cardiovascular and respiratory systems in an intensive care unit. There is no specific antidote. Haemodialysis may be useful.

[redacted]

### *2.5.5.3 Contraindications*

Ethosuximide is contraindicated in patients with hypersensitivity to the active substance and other succinimides. [redacted]

Ethosuximide is contraindicated during breastfeeding. [redacted]

### *2.5.5.4 Warnings and Precautions*

If dyskinesias occur, ethosuximide must be discontinued and diphenhydramine administered by the intravenous route, if required.

Special attention should be given to clinical symptoms of bone marrow damage (fever, angina, haemorrhage). It is recommended to check the blood count regularly (initially monthly, after one year every six months) to identify potential bone marrow damage. At a leucocyte count of less than 3500/mm3 or a granulocyte ratio of less than 25%, the dose should be reduced or the therapy discontinued. The liver enzymes should also be checked regularly.

In particular in patients with a history of psychiatric disorders psychic undesirable effects, paranoid and hallucinatory symptoms, anxiety, agitation) may occur, therefore special caution is required when treating this group of patients with ethosuximide.

**Suicidal ideation and behaviour**

Suicidal thoughts and behaviour have been reported in patients treated with anti-epileptics for various indications. A meta-analysis of randomised, placebo-controlled studies with antiepileptics also showed a slightly increased risk for suicidal thoughts and behaviour. The mechanism triggering this undesirable effect is unknown, and the data available do not exclude a potentially increased risk when taking ethosuximide.

Therefore, patients should be monitored for the emergence of suicidal thoughts and behaviour, and an appropriate treatment should be considered. Patients (and their caregivers) should be advised to seek medical help if symptoms of suicidal thoughts or behaviour occur.

Note:

To prevent grand fits which are often associated with complex and atypical absences, ethosuximide can be combined with effective anticonvulsives (e.g. primidone or phenobarbital). Additional grand mal prophylaxis can be dispensed with only in the case of pyknoleptic absence epilepsies in children of school age.

[redacted]

### *2.5.5.5 Effects on ability to drive and use machines*

During the adjustment phase, at higher doses and in combination with other medicinal products affecting the central nervous system reactivity can be impaired to an extent that the ability to drive or operate machines is affected. This may even be the case when ethosuximide is taken as prescribed, and especially in connection with alcohol. Therefore patients should not drive,

operate machines or perform any other potentially hazardous activities, at least not during the adjustment phase of the treatment. The decision will be taken in each case by the attending doctor considering the patient's individual response and the respective dose. [redacted]

## 2.5.6 BENEFITS AND RISKS CONCLUSIONS

The applicant intends to file an application for marketing authorization of for Ethosuximide 250 mg/5 ml oral solution in accordance with 2004/27/EC as an amendment to Article 10.1(a) (iii) of council directive 2001/83/EC based on well established.

The applicant's Ethosuximide 250 mg / 5 mL Oral Solution is a generic product of the proprietary medicinal product, reference product, Zarontin® (Ethosuximide 250 mg/5mL Sirop 200 mL) of Essential Pharma Ltd., for which the marketing authorization is granted.

The proposed indication of the applicant's product as below is same as approved indication of the available reference product in the market:

- *Pyknoleptic absences as well as complex and atypical absences.*
- *Myoclonic-astatic petit mal and myoclonic fits of adolescents (impulsive petit mal), if other medicinal products are not effective and/or are not tolerated.*

The applicant has conducted a bioequivalence study in healthy subjects under fasting conditions and the test formulation Ethosuximide 250 mg / 5 mL Oral Solution was found to be bioequivalent with reference product, Zarontin® (Ethosuximide 250 mg/5mL Sirop 200 mL) of Essential Pharma Ltd., 7 Eghm Business Village Crabtree Road, Egham Surrey Tw20 8rb Royaume-Uni.

**Pharmacodynamics**

Ethosuximide (α-ethyl-α-methyl succinimide) an antiepileptic drug of succinimide derivatives, primarily acts by blocking T-type voltage-gated calcium channels in thalamic neurones. The drugs also share a very unique mechanism among antiepileptic drugs by reducing the overproduction of nitric oxide and free radicals, which may be related to its anticonvulsant and neuroprotective effects.

Pretreatment and ongoing behavioral problems exist in childhood absence epilepsy. Valproic acid was reported to be show worse behavioral outcomes in children than ethosuximide or lamotrigine, further reinforcing ethosuximide as the preferred initial therapy.

**Pharmacokinetics**

Ethosuximide is completely absorbed after oral administration from the gastrointestinal tract with maximum concentration achieved in 3 to 7 hours. The drug bioavailability is 95 – 100%. The rate of absorption following administration of ethosuximide syrup tends to be faster than

after capsules; however the bioavailability of the two formulations is equivalent. Steady state levels are expected to occur 8-10 days after start of treatment. The kinetics of ethosuximide is linear, so that plasma concentrations increase in proportion to increasing dose.

Ethosuximide is not bound to plasma proteins, and it is present in the cerebrospinal fluid, saliva, and tears at concentrations similar to those found in plasma. The volume of distribution of ethosuximide is 0.7 L/kg, and thus it is distributed through body. Ethosuximide passes the placenta barrier, and its plasma levels in neonates are similar to those in the mother. In report involving 10 epileptic mothers treated with ethosuximide and their newborns, the ratios of the fetal/maternal serum levels and milk/maternal serum levels were 0.97 ± 0.02 and 0.86 ± 0.08, respectively.

Ethosuximide is extensively metabolized in the liver by oxidation to metabolities, namely, 2-(1-hydroxyethyl)-2-methyl succinimide, 2-ethyl-2-methyl-3-hydroxysuccinimide, 2-(1-bydroxyethyl)-2-methylsuccinimides, 2-acetyl-2-methylsuccinimide and 2-carboxymethyl-2-methylsuccinimide. Approximately 80% of ethosuximide undergoes hepatic metabolism and remainder, around 20% of an administered dose of ethosuximide, is excreted unchanged in the urine.

In adults, the elimination t1/2 of ethosuximide is 40–60 h, while in children it is 29–39 h. Pharmacokinetic study in patients suggests that the disposition of ethosuximide in humans is not stereoselective and that the measurement of total concentrations of ethosuximide is sufficient for therapeutic monitoring.

The drug was rapidly cleared by hemodialysis in patients with chronic renal disease suggesting the usefulness of dialysis in the treatment of ethosuximide overdosage. Long-term treatment of children at 20 mg/kg body weight produces a plasma concentration of approximately 50 μg/ ml. In children an oral daily dose of 1 mg/kg produces a plasma concentration of 1-2 μg/ml. Therefore, younger children require a slightly higher dose than older children. No statistically significant differences in the plasma concentration of ethosuximide were reported in patients under 10 years of age **(**14 subjects) and in patients over 15 years of age (20 subjects).

**Drug interactions**

Because ethosuximide is frequently combined with valproic acid, the possibility of a pharmacokinetic interaction between the two antiepileptic drugs has been extensively investigated. The interaction is bidirectional, in that plasma valproic acid concentrations are

reduced by ethosuximide, while valproic acid has been reported to both increase and decrease plasma ethosuximide concentrations. The most clinically significant interaction with ethosuximide relates to the enhancement of ethosuximide metabolism by enzyme-inducing AEDs, resulting in lower plasma ethosuximide concentrations.
Ethosuximide normally does not change the plasma concentration of other anti-epileptics such as primidone, phenobarbital and phenytoin. The concomitant administration of carbamazepine, methylphenbbatbitone and rifampicin increases the plasma clearance of ethosuximide. Ethosuximide disposition is altered by carbamazepine.

The simultaneous use of medicinal products affecting the central nervous system, alcohol or convulsion-inducing substances and ethosuximide should be avoided. A drug interaction study of ethosuximide with contraceptive hormones revealed that ethosuximide does not interact significantly with oral contraceptives. Suximides do not have enzyme-inducing properties so it is unlikely that there will be significant drug interactions with the combined oral contraceptive pill.

**Efficacy**

Ethosuximide is one of the drugs of choice in the treatment of absence seizures. Several reports have been published on the efficacy of anti-epileptic drugs in the treatment of typical absence seizures or childhood absence epilepsy. The efficacy of ethosuximide and valproic acid was equal in the treatment of typical absence seizures. A double blind randomized controlled clinical trial found that ethosuximide and valproic acid was more effective than lamotrigine. Comparison of long–term efficacy showed that ethosuximide, valproic acid and lamotrigine were equally efficacious. However, the onset of efficacy was faster for ethosuximide compared with valproic acid lamotrigine.

Based on the CAE trial, ethosuximide is the drug of choice as initial monotherapy for CAE, when absence seizures are the only seizure type. Ethosuximide is reported to be a valuable adjunctive treatment for epileptic falling spells that occur in the context of multiple seizure types. Ethosuximide proved to be extremely effective in controlling epileptic negative myoclonus associated with childhood partial epilepsies, within 1 month of the gradual introduction of ethosuximide. Ethosuximide introduction was shown to be effective in improving seizure frequency in all subjects, with disappearance of seizures in five patients and a 75% reduction in seizure frequency in the remaining children.
A small trial in 09 paediatric patients suggest that ethosuximide is effective in the treatment of epileptic negative myoclonus and that it should be considered as a first-choice drug in the treatment of this motor disorder. Thirty-seven patients with previously untreated absence seizures were treated with ethosuximide. Seizures were completely controlled in 7 patients (19%); 90 to 100 percent control was achieved in 18 patients (49%) and 50 to 100 percent

control in 35 (95%). An initial observational study of ethosuximide conducted over a mean of 37 weeks of treatment found that 42% of 109 patients had complete seizure control, with an additional 24% having had 80–99% reduction in seizures. In patients characterized as pure absence epilepsy, 61% had complete control.
A Cochrane review was conducted to report the evidence for the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures, when compared with placebo or each other. Authors concluded that with regards to both efficacy and tolerability, ethosuximide represents the optimal initial empirical monotherapy for children and adolescents with absence seizures.

**Safety**

Although ethosuximide is highly efficacious in the treatment of absence seizures, it is associated with gastrointestinal and central nervous system side-effects. Nausea, abdominal discomfort, vomiting, diarrhea, hiccups and anorexia are common at the onset of ethosuximide therapy. Central nervous system effects include drowsiness, dizziness, fatigue, insomnia, tiredness, headache, sedation and ataxia. Rarely, clinically apparent behavioral disturbances may occur, including nervousness, irritability, depression, hallucinations, and even psychosis.

Ethosuximide has been also associated with a wide variety of idiosyncratic reactions, including allergic dermatitis, rash, Stevens-Johnson syndrome, lupus-like syndrome, serum sickness reaction, agranulocytosis, and aplastic anemia. Hematopoietic adverse effects include leukopenia, agranulocytosis, eosinophilia, and pancytopenia. Ethosuximide-induced agranulocytosis was observed in a 16-month-old male infant with Down syndrome. Ethosuximide induced lupus is a rare adverse drug reaction, appearing in the medical literature mostly as single case reports. Symptoms typically resolve with cessation of ethosuximide, but recovery may be prolonged. Other idiosyncratic adverse drug reactions include allergic rashes, which typically resolve with medication withdrawal.

In paediatric study involving 175 patients, side effects included gastrointestinal symptoms, headache, drowsiness, and dizziness. A double-blind, randomized controlled clinical trial compared the tolerability of ethosuximide, valproic acid and lamotrigine in children with newly diagnosed childhood absence epilepsy. Overall, the most common of these 20 different adverse events were fatigue and headache. Stomach upset, nausea, and vomiting occurred more frequently (defined as 5% greater occurrence in one treatment group compared to either of the other treatment groups) in the ethosuximide group. The study concluded that ethosuximide is the most optimal treatment because it is associated with a lower risk of adverse effects on attention.

Long term tolerability of ethosuximide, valproic acid and lamotrigine as initial monotherapies was evaluated in patients with newly diagnosed childhood absence epilepsy. The frequent or specific adverse events associated with AEDs were drowsiness and gastrointestinal complaints, such as nausea, vomiting, and abdominal pain, for ethosuximide and valproic acid, alopecia for valproic acid, and rash for lamotrigine.
Ethosuximide is contraindicated in patients with hypersensitivity to the active substance and other succinimides. The drug is also contraindicated during breastfeeding. Women of childbearing potential should be advised by their doctor of the necessity of planning and monitoring a pregnancy before starting the treatment with ethosuximide.

The treatment with ethosuximide should not be interrupted during pregnancy without the consent of a physician as the sudden discontinuation of the treatment or uncontrolled reduction of the dose may result in recurrence of epileptic seizures which may harm the pregnant woman and/or the unborn child. Ethosuximide crosses the placenta. Patients should be informed of the increased risk of malformations and prenatal diagnostic measures should be offered. Most common malformations reported are cleft lip, cardiovascular malformations and neural tube defects.

Breast-feeding should be discontinued during treatment with ethosuximide. Ethosuximide is considered to be potentially dangerous during lactation and monitoring breastfed infant has been suggested.

**Conclusion**

From the available safety profile of Ethosuximide 250 mg / 5 mL Oral Solution, it is clearly evident that the side effects are known and dose-dependent and definite treatment is available for any side effect. No new or unexpected safety concerns could arise from the use of generic product.

Clinical experience with ethosuximide has shown it to be effective in most cases of typical absence epilepsy and the side effects are few, mild and treatable. It was also shown that ethosuximide is an effective drug, with few side effects, in the treatment of most cases of typical absence epilepsy in children.

Based on the Bioequivalence study results, it is concluded that Ethosuximide 250 mg / 5 mL Oral Solution of [redacted]

The proposed applicant SmPC is in line with the reference product.

In conclusion, use of the applicant's Ethosuximide 250 mg / 5 mL Oral Solution according to the instructions does not constitute risk to a patient or the community providing that contraindications, precautions and possible interactions are adequately taken into account.

[redacted]

[redacted]

[redacted]

[redacted]