LEVEXA
Levetiracetam
Injection

COMPOSITION :
LEVEXA Injection 100 mg/mL, each mL contains : Levetiracetam 100 mg.

Description of the dosage form
LEVEXA Injection 100 mg/mL is a clear colorless solution in Type 1, 5 mL tubular glass vials sealed with 20 mm grey serum rubber stoppers and blue color flip off aluminum seal.
The excipients ingredients include sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection.

PHARMACOLOGY :
Mechanism of action
The active substance, Levetiracetam, is a pyrrolidone derivative (S-enantiomer of alfa-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. The mechanism of action of Levetiracetam still remains to be fully elucidated. In vitro and in vivo experiments suggest that Levetiracetam does not alter basic cell characteristic and normal neurotransmission.
In vitro studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, Levetiracetam has been shown in in vitro studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti -seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacokinetics (Levetiracetam Tablet)
This study was designed as a randomized, single blind, two periods, single dose, two-period, two-treatment, two-sequence, cross-over study with one week washout period in 13 healthy subjects under fasting condition. The study was conducted following an oral administration of one tablet 500 mg of the test drug or one tablet of the reference drug.
Based on the pharmacokinetic parameters of Levetiracetam (N = 13), mean ± SD for Test Drug showed : C_{max} values were 15237.76 (2904.20) $ng.mL^{-1}$, respectively; AUC_t values were 139403.22 (17593.31) $h.ng.mL^{-1}$; AUC_{inf} values were 160734.19 (20883.14); T_{max} values were 0.81 (0.29) hour; $T_{1/2}$ values were 8.31 (0.77) hour.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Results from bioequivalence study for Test Drug were as following : 90.00% Confidence Intervals of geometric means ratio of the two bioavailability parameters of Levetiracetam were 91.86 – 106.40% for C_{max} and 95.66 – 101.11% for AUC_t. Intra subject CV (%) of C_{max} and AUC_t for Levetiracetam were 10.40 and 3.92%, respectively.
Conclusion : These results showed that 500 mg Levetiracetam film coated tablet was bioequivalent to the reference product.

Pharmacokinetic (Levetiracetam injection)

Overview

Levetiracetam is rapidly and almost completely absorbed after oral administration. Levetiracetam injection and tablets are bioequivalent. Levetiracetam injection and tablets are bioequivalent. The pharmacokinetics of Levetiracetam are linear and time-invariant, with low intra- and inter-subject variability. Levetiracetam is not significantly protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of Levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renally excreted. Plasma half-life of levetiracetam across studies is approximately 6 - 8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Distribution

The equivalence of Levetiracetam injection and the oral formulation was demonstrated in a bioavailability study of 17 healthy volunteers. In this study, Levetiracetam 1500 mg was diluted in 100 mL 0.9% sterile saline solution and was infused over 15 minutes. The time independent pharmacokinetic profile of Levetiracetam was demonstrated following 1500 mg intravenous infusion for 4 days with BID dosing. The $AUC_{(0-12)}$ at steady-state was equivalent to AUC_{inf} following an equivalent single dose. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Elimination
Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose, route of administration or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/minute/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment.

INDICATIONS :
Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in patients with epilepsy.
Limitations of use : Levetiracetam injection is for intravenous use only as an alternative for patients when oral administration is temporary not feasible.

CONTRAINDICATIONS :
Levetiracetam is contraindicated in patients with hypersensitivity to the active substance or other pyrrolidine derivatives or to any of the excipients.

DOSAGE AND ADMINISTRATIONS :
Dosing for partial-onset seizures
The recommended dosing for monotherapy and adjunctive therapy is the same as outlined below.
There is no clinical study experience with administration of intravenous Levetiracetam for a period longer than 4 days.

Adults 16 years of age and older
Initiate treatment with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Switching from Oral Dosing
When switching from oral Levetiracetam, the initial total daily intravenous dosage of Levetiracetam should be equivalent to the total daily dosage and frequency of oral Levetiracetam.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Switching to Oral Dosing
At the end of the intravenous treatment period, the patient may be switched to Levetiracetam oral administration at the equivalent daily dosage and frequency of the intravenous administration.

Preparation and Administration Instructions
Levetiracetam injection is for intravenous use only and should be diluted in 100 mL of a compatible diluent prior to administration. If a smaller volume is required, the amount of diluent should be calculated to not exceed a maximum Levetiracetam concentration of 15 mg per mL of diluted solution. Consideration should also be given to the total daily fluid intake of the patient. Levetiracetam injection should be administered as a 15-minute IV infusion. One vial of Levetiracetam injection contains 500 mg Levetiracetam (500 mg/5 mL).

Levetiracetam injection may be mixed with the following diluents. The reconstituted solution is stable up to 24 hours at temperature below 30°C during compatibility study with the diluents.
Diluents :
- Sodium chloride 0.9%
- Lactated Ringer's injection
- Dextrose 5% injection

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Product with particulate matter or discoloration should not be used.
Any unused portion of the Levetiracetam injection vial contents should be discarded.

Adults
See Table 1 for the recommended preparation and administration of Levetiracetam injection for adults to achieve a dose of 500 mg, 1000 mg, or 1500 mg.
Table 1 : Preparation and administration of Levetiracetam Injection

Dose	**Withdraw Volume**	**Volume of Diluent**	**Infusion time**
500 mg	5 mL (5 mL vial)	100 mL	15 minutes
1000 mg	10 mL (two 5 mL vial)	100 mL	15 minutes
1500 mg	15 mL (three 5 mL vial)	100 mL	15 minutes

For example, to prepare a 1000 mg dose, dilute 10 mL of Levetiracetam injection in 100 mL of a compatible diluent and administer intravenously as a 15-minute infusion.

Dosage Adjustments in Adult Patients with Renal Impairment
Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults with renal impairment are shown in Table 2. In

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

order to calculate the dose recommended for adult patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CLcr) in mL/minute must first be calculated using the following formula:

$$CLcr = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Then CLcr is adjusted for body surface area (BSA) as follows :

$$CLcr\ (mL/min/1.73m^2) = \frac{CLcr\ (mL/min)}{BSA\ subject\ (m^2)} \times 1.73$$

Table 2 : Dosage adjustment regimen for adult patients with impaired renal function

Group	**Creatinine Clearance (mL/min)**	**Dosage (mg)**	**Frequency**
Normal	> 80	500 to 1500	Every 12 hours
Mild	50 – 79	500 to 1000	Every 12 hours
Moderate	30 – 49	250 to 750	Every 12 hours
Severe	< 30	250 to 500	Every 12 hours
ESRD patients using dialysis	----	500 to 1000	Every 24 hours[1]

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

Discontinuation of Levetiracetam

Avoid abrupt withdrawal from Levetiracetam in order to reduce the risk of increased seizure frequency and status epilepticus.

WARNINGS AND PRECAUTIONS :

Electrocardiogram QT interval prolongation

Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with Q-Tc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant preexisting cardiac disease or electrolyte disturbances.

Worsening seizures

As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Suicide
Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including Levetiracetam). A meta-analysis of randomized placebo-controlled trials of antiepileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known. Therefore, patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour

Acute kidney injury
The use of Levetiracetam has been rarely associated with acute kidney injury, with a time to onset ranging from a few days to severe months.

Behavioral abnormalities and psychotic symptoms
Levetiracetam may cause psychotic symptoms and behavioral abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviors are noticed, treatment adaption or gradual discontinuation should be considered. If discontinuation is considered, please see Discontinuation of Levetiracetam.

Somnolence and Fatigue
Levetiracetam may cause somnolence and fatigue. Patients should be monitored for somnolence and fatigue, and be advised not to drive or operate machinery until they have gained sufficient experience on Levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.

Anaphylaxis and Angioedema
Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the post-marketing setting have included hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. In some reported cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, Levetiracetam should be discontinued and the patient should seek immediate medical attention. Levetiracetam should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Serious Dermatological Reactions
Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in adult patients treated with Levetiracetam. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with Levetiracetam has also been reported. Levetiracetam should be discontinued at

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Coordination Difficulties

Levetiracetam may cause coordination difficulties. Patients should be monitored for signs and symptoms of coordination difficulties and advised not to drive or operate machinery until they have gained sufficient experience on Levetiracetam to gauge whether it could adversely affect their ability to drive or operate machinery.

Withdrawal Seizures

As with most antiepileptic drugs, Levetiracetam should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. But if withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Hematologic Abnormalities

Levetiracetam can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in white blood cell (WBC), neutrophil, and red blood cells counts (RBC); decreases in hemoglobin and hematocrit; and increases in eosinophil counts. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported in the post-marketing setting. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.

Partial-Onset Seizures

Adults

In adult patients with partial-onset seizures, minor but statistically significant decreases in total mean RBC, mean hemoglobin, and mean hematocrit, were seen in Levetiracetam-treated patients.

Seizure Control During Pregnancy

Physiological changes may gradually decrease plasma levels of Levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

PATIENT COUNSELING INFORMATION

- Psychiatric reactions and changes in behavior : Advise patients and their caregivers that Levetiracetam may cause changes in behavior (e.g., aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms.
- Effects on driving or operating machinery : Inform patients that Levetiracetam may cause dizziness and somnolence. Inform patients not to drive or operate machinery until they have gained sufficient experience on Levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

- Anaphylaxis and angioedema : Advise patients to discontinue Levetiracetam and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema.
- Dermatological adverse reactions : Advise patients that serious dermatological adverse reactions have occurred in patients treated with Levetiracetam and instruct them to call their physician immediately if a rash develops.
- Withdrawal of Levetiracetam : Advise patients and caregivers not to discontinue use of Levetiracetam without consulting with their healthcare provider. Levetiracetam should normally be gradually withdrawn to reduce the potential of increased seizure frequency and status epilepticus.
- Pregnancy : Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during Levetiracetam therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry if they become pregnant.

USE IN SPECIFIC POPULATIONS

Pregnancy

Levetiracetam blood levels may decrease during pregnancy.

Physiological changes during pregnancy may affect Levetiracetam concentration. Decrease in Levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester. Dose adjustments may be necessary to maintain clinical response.

While available studies cannot definitively establish the absence of risk, data from the published literature and pregnancy registries have not established an association with Levetiracetam use during pregnancy and major birth defects or miscarriage.

Pregnancy category C : There are no adequate and well-controlled studies in pregnant women. In animal studies, Levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Levetiracetam is excreted in human milk. There are no data on the effects of Levetiracetam on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Levetiracetam and any potential adverse effects on the breastfed infant from Levetiracetam or from the underlying maternal condition.

Geriatric Use

Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment

Clearance of Levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Dosage adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis.

DRUG INTERACTIONS :

Phenytoin

Levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of Phenytoin in patients with refractory epilepsy. Pharmacokinetics of Levetiracetam were also not affected by Phenytoin.

Valproate

Levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of Valproate. Valproate 500 mg twice daily did not modify the rate or extent of Levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

Other Antileptic drugs

Potential drug interactions between Levetiracetam and other AEDs (Carbamazepine, Gabapentin, Lamotrigine, Phenobarbital, Phenytoin, Primidone and Valproate) were also assessed by evaluating the serum concentrations of Levetiracetam and these AEDs. These data indicate that Levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of Levetiracetam.

Oral contraceptives

Levetiracetam (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg Ethinyl estradiol and 0.15 mg Levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of Levetiracetam.

Digoxin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of Digoxin given as a 0.25 mg dose every day. Coadministration of Digoxin did not influence the pharmacokinetics of Levetiracetam.

Warfarin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics of R and S Warfarin. Prothrombin time was not affected by Levetiracetam. Coadministration of Warfarin did not affect the pharmacokinetics of Levetiracetam.

Probenecid

The effect of Levetiracetam on Probenecid was not studied.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Methotrexate
Concomitant administration of Levetiracetam and Methotrexate has been reported to decrease Methotrexate clearance, resulting in increased/prolonged blood Methotrexate concentration to potentially toxic levels. Blood Methotrexate and Levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.
Laxatives
There have been isolated reports of decreased Levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral Levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking Levetiracetam.
Food and alcohol
The extent of absorption of Levetiracetam was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of Levetiracetam with alcohol are available.

ADVERSE DRUG REACTIONS :
Adverse drug reaction (ADRs) are listed below by MedDRA system organ class by frequency.
Frequencies are defined as :
Very common >= 1/10;
Common >= 1/100 to 1/10;
Uncommon >= 1/1000 to =1/10000 to =1/1000

Infections and infestations
Very common : Nasopharyngitis
Rare : Infections

Blood and lymphatic system disorders
Uncommon : Thrombocytopenia, leukopenia
Rare : Pancytopenia, neutropenia, agranulocytosis

Immune system disorders
Rare : Drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)

Metabolism and nutrition disorders
Common : Anorexia
Uncommon : Weight decreased, weight increase
Rare : Hyponatraemia

Psychiatric disorders
Common : Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability
Uncommon : Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation
Rare : Completed suicide, personality disorder, thinking abnormal, delirium

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Nervous system disorders
Very common : Somnolence, headache
Common : Convulsion, balance disorder, dizziness, lethargy, tremor
Uncommon : Amnesia, memory impairment, coordination abnormal ataxia, paraesthesia, disturbance in attention
Rare : Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated

Eye disorders
Uncommon : Diplopia, vision blurred

Ear and labyrinth disorders
Common : Vertigo

Cardiac disorders
Rare : Electrocardiogram QT Prolonged

Respiratory, thoracic and mediastinal disorders
Common : Cough

Gastrointestinal disorders
Common : Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea
Rare : Pancreatitis

Hepatobiliary disorders
Uncommon : Liver function test abnormal
Rare : Hepatic failure, hepatitis

Renal and urinary disorders
Rare : Acute kidney injury

Skin and subcutaneous tissue disorders
Common : Rash
Uncommon : Alopecia, eczema, pruritus
Rare : Toxic epidermal necrolysis, steven-johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders
Uncommon : Muscular weakness, myalgia
Rare : Rhabdomyolysis and blood creatine phosphokinase increase*

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

General disorders and administration site conditions
Common : Asthenia/fatigue

Injury, poisoning and procedural complications
Uncommon : Injury

*prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions
The risk of anorexia is higher when Levetiracetam is co-administered with Topiramate.
In several cases of alopecia, recovery was observed when Levetiracetam was discontinued.
Bone marrow suppression was identified in some of the cases of pancytopenia.
Case of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

OVERDOSAGE :
There is no specific antidote for overdose with Levetiracetam.
Hemodialysis : Standard hemodialysis procedures result in significant clearance of Levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.
Symptoms and signs : Somnolence, agitation, aggression, depressed level of consciousness, respiratory and depression and coma were observed with Levetiracetam overdoses.

STORAGE :
Store below 30°C. Keep out of reach of children.

PRESENTATION :
LEVEXA Injection 100 mg/mL
Box, 1 vial @ 5 mL
Reg. No. …

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

Manufactured by :
ASPIRO PHARMA LIMITED
Telangana – India

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Imported and marketed by :
PT. AMAROX PHARMA GLOBAL
Bekasi – Indonesia

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EREG10042512100098

INFORMASI PRODUK UNTUK PASIEN

LEVEXA
Levetiracetam
Injection

Bacalah seluruh brosur ini dengan saksama sebelum Anda mulai menggunakan obat ini karena brosur ini berisi informasi yang penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker, atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Jika Anda mengalami efek samping, diskusikan dengan dokter, apoteker, atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat Bagian 4.

Apa yang terdapat di dalam brosur ini :

1. Apa itu LEVEXA dan kegunaannya ?

LEVEXA mengandung zat aktif Levetiracetam, merupakan obat yang digunakan sebagai terapi tambahan dalam pengobatan kejang onset parsial dengan atau tanpa generalisasi sekunder pada pasien dengan epilepsi.

Batasan Penggunaan : Injeksi Levetiracetam hanya untuk penggunaan intravena sebagai alternatif bagi pasien ketika pemberian oral sementara tidak memungkinkan.

2. Apa yang perlu Anda ketahui sebelum menggunakan LEVEXA ?

Jangan menggunakan LEVEXA : Jika Anda alergi (hipersensitif) terhadap Levetiracetam atau turunan pirolidin lainnya atau terhadap bahan lainnya dalam obat ini.

Peringatan dan perhatian

Diskusikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan **LEVEXA** :

- **LEVEXA** dapat menyebabkan perpanjangan interval QT elektrokardiogram terutama pada pasien yang diobati secara bersamaan dengan obat yang mempengaruhi interval

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

QTc, atau pada pasien dengan penyakit jantung atau gangguan elektrolit yang sudah ada sebelumnya.

- Terdapat laporan bahwa **LEVEXA** dapat memperburuk kejadian kejang secara paradoks. Hal ini dapat terjadi dibulan pertama setelah pemberian Levetiracetam atau pada penggunaan dosis yang berlebihan dan reversibel pada penghentian obat atau penurunan. Mohon untuk mendiskusikannya terlebih dahulu dengan dokter Anda.
- **LEVEXA** dapat menimbulkan reaksi psikiatri dan perubahan perilaku. Levetiracetam dapat menyebabkan perubahan perilaku (misalnya, agresi, agitasi, kemarahan, kecemasan, apatis, depresi, *hostility* (perasaan negatif/permusuhan), dan lekas marah dan gejala psikotik. Pasien yang diobati dengan Levetiracetam harus dipantau untuk tanda dan gejala kejiwaan. Oleh karena itu Dokter perlu menginformasikan kepada pasien dan pengasuh mereka mengenai efek tersebut sebelum pemberian injeksi **LEVEXA**.
- **LEVEXA** dapat menyebabkan rasa mengantuk dan kelelahan. Oleh karena itu, pasien disarankan untuk tidak mengemudi atau mengoperasikan mesin. Pasien disarankan untuk tidak mengemudi atau mengoperasikan mesin sampai mereka memperoleh pengalaman yang cukup tentang Levetiracetam untuk mengukur apakah hal itu mempengaruhi kemampuan mereka untuk mengemudi atau mengoperasikan mesin.
- **LEVEXA** dapat menyebabkan anafilaksis atau angioedema (pembengkakan) setelah dosis pertama atau setiap saat selama pengobatan. Tanda dan gejala dalam kasus yang dilaporkan termasuk hipotensi, gatal-gatal, ruam, gangguan pernapasan, dan pembengkakan pada wajah, bibir, mulut, mata, lidah, tenggorokan, dan kaki. Jika pasien mengalami tanda atau gejala anafilaksis atau angioedema, Levetiracetam harus dihentikan dan pasien harus mencari perhatian medis segera. Mohon untuk mendiskusikannya terlebih dahulu dengan dokter Anda sebelum memutuskan penggunaan obat ini.
- **LEVEXA** dapat menyebabkan reaksi dermatologis yang serius seperti Steven-Johnson syndrome (SJS) dan nekrolisis epidermal toksik (TEN) yang telah dilaporkan pada pasien dewasa yang diobati dengan Levetiracetam. Pasien disarankan untuk segera menghubungi dokter jika timbul ruam.
- **LEVEXA** harus dihentikan pada tanda pertama ruam, kecuali ruam tersebut jelas tidak terkait dengan obat. Jika tanda atau gejala menunjukkan SJS/TEN, penggunaan obat ini tidak boleh dilanjutkan dan terapi alternatif harus dipertimbangkan.
- **LEVEXA** dapat menyebabkan kesulitan koordinasi (sulit mengoordinasikan gerakan). Pasien harus dipantau untuk tanda dan gejala kesulitan koordinasi dan disarankan untuk tidak mengemudi atau mengoperasikan mesin sampai mereka mendapatkan pengalaman yang cukup tentang Levetiracetam untuk mengukur apakah itu dapat mempengaruhi kemampuan mereka untuk mengemudi atau mengoperasikan mesin.
- **LEVEXA** dapat menyebabkan kelainan hematologi (kelainan pada darah). Kelainan hematologi yang terjadi seperti penurunan sel darah putih (WBC), neutrofil, dan jumlah sel darah merah (RBC); penurunan hemoglobin dan hematokrit; dan peningkatan jumlah eosinofil. Kasus agranulositosis, pansitopenia, dan trombositopenia telah dilaporkan. Hitung darah lengkap dianjurkan pada pasien yang mengalami kelemahan yang signifikan, demam, infeksi berulang, atau gangguan koagulasi (gangguan pembekuan darah).

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

- Perubahan fisiologis dapat menurunkan kadar plasma Levetiracetam secara bertahap selama kehamilan. Penurunan ini lebih terasa selama trimester ketiga. Dianjurkan agar pasien dipantau dengan hati-hati selama kehamilan. Pemantauan ketat harus dilanjutkan selama periode *postpartum* (masa nifas) terutama jika dosis diubah selama kehamilan. Pasien harus memberitahu penyedia layanan kesehatan mereka jika mereka hamil atau berniat untuk hamil selama terapi Levetiracetam.
- **LEVEXA** dapat menurunkan bersihan Levetiracetam pada pasien dengan gangguan ginjal dan berkaitan dengan klirens kreatinin. Penyesuaian dosis dianjurkan untuk pasien dengan gangguan fungsi ginjal dan dosis tambahan harus diberikan kepada pasien setelah dialisis.

Silakan konsultasikan dengan dokter Anda, meskipun pernyataan-pernyataan di atas hanya pernah Anda alami di masa lampau.

Usia lanjut
- **LEVEXA** diketahui memiliki risiko reaksi merugikan terhadap obat ini mungkin lebih besar pada pasien dengan gangguan fungsi ginjal. Karena pasien usia lanjut lebih cenderung mengalami penurunan fungsi ginjal, pemilihan dosis harus hati-hati, dan mungkin berguna untuk memantau fungsi ginjal.

Gangguan ginjal
- Dikarenakan bersihan **LEVEXA** dapat menurun pada pasien dengan gangguan ginjal maka diperlukan penyesuaian dosis untuk pasien dengan gangguan fungsi ginjal dan dosis tambahan harus diberikan kepada pasien setelah dialisis. Mohon pasien mendiskusikannya dengan dokter

Obat-obatan lain dan LEVEXA
Sampaikan kepada dokter, apoteker, atau perawat Anda jika Anda sedang mendapat, baru saja mendapat, atau mungkin menggunakan obat-obatan lainnya.

Kehamilan, menyusui, dan kesuburan
Peningkatan Levetiracetam dalam darah dapat menurun selama kehamilan. Perubahan fisiologis selama kehamilan dapat mempengaruhi konsentrasi Levetiracetam dalam darah dimana penurunan ini lebih terlihat pada trimester ketiga. Penyesuaian dosis diperlukan untuk menjaga respon klinis.
Levetiracetam diekskresikan kedalam ASI. Oleh karena itu, manfaat perkembangan dan kesehatan Ibu yang menyusui harus dipertimbangkan bersama dengan kebutuhan klinis Ibu/pasien, potensi efek samping pada bayi yang diberikan ASI maupun kondisi pasien. Untuk informasi selengkapnya, mohon konsultasikan dengan dokter Anda. Mintalah saran kepada dokter, apoteker, atau perawat Anda sebelum menggunakan obat apa pun.

Kemampuan berkendara dan menggunakan mesin
LEVEXA belum terbukti mengurangi kemampuan Anda dalam berkendara atau menggunakan alat-alat atau mesin apa pun. Namun, rasa kantuk dan kelelahan (*fatigue*) telah dilaporkan terjadi pada penggunaan **LEVEXA**. Jika Anda mengalami gejala-gejala yang memengaruhi penglihatan atau konsentrasi Anda, atau kemampuan Anda untuk

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

bereaksi, jangan berkendara dan menggunakan mesin sampai gejala-gejala tersebut mereda.

Meminum obat-obatan lainnya
Beritahukan dokter Anda apabila Anda sedang meminum atau baru-baru ini meminum salah satu dari obat-obatan berikut ini :

- **Methotrexate**
  Pemberian Levetiracetam dan Methotrexate secara bersamaan dapat menurunkan bersihan Methotrexate, yang mengakibatkan peningkatan/perpanjangan konsentrasi Methotrexate darah ke tingkat yang berpotensi toksik. Kadar Methotrexate dan Levetiracetam dalam darah harus dipantau secara hati-hati pada pasien yang diobati secara bersamaan dengan kedua obat tersebut.
- **Pencahar**
  Terdapat laporan kejadian dari penurunan kemanjuran Levetiracetam ketika obat pencahar osmotik seperti Macrogol telah diberikan secara bersamaan dengan Levetiracetam oral. Oleh karena itu, Macrogol tidak boleh dikonsumsi secara oral selama satu jam sebelum dan satu jam setelah mengonsumsi Levetiracetam.
- **Makanan dan alkohol**
  Tingkat penyerapan Levetiracetam tidak diubah oleh makanan, tetapi tingkat penyerapannya sedikit berkurang. Tidak ada data tentang interaksi Levetiracetam dengan alkohol yang tersedia.

Beritahukan dokter atau apoteker Anda apabila Anda sedang meminum atau baru mendapatkan obat-obatan lain termasuk obat-obatan yang didapatkan tanpa resep dokter.

3. Cara penggunaan LEVEXA

Dosis dan frekuensi pemberian
Dosis untuk kejang onset parsial
Dosis yang direkomendasikan untuk monoterapi dan terapi tambahan adalah sama seperti yang diuraikan di bawah ini.
Tidak ada pengalaman studi klinis dengan pemberian Levetiracetam intravena untuk jangka waktu lebih dari 4 hari.

<u>Dewasa berusia diatas 16 tahun</u>
Memulai pengobatan dengan dosis harian 1000 mg/hari, diberikan sebagai dosis dua kali sehari (500 mg dua kali sehari). Penambahan dosis tambahan dapat diberikan (1000 mg/hari tambahan setiap 2 minggu) hingga dosis harian maksimum yang direkomendasikan 3000 mg. Tidak ada bukti bahwa dosis lebih besar dari 3000 mg/hari memberikan manfaat tambahan.

Peralihan dari dosis oral
Ketika beralih dari Levetiracetam oral, dosis awal harian total Levetiracetam intravena harus setara dengan dosis harian total dan frekuensi dari Levetiracetam oral.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Peralihan ke dosis oral
Pada akhir masa pengobatan intravena, pasien dapat dialihkan ke pemberian oral Levetiracetam dengan dosis harian yang setara dan frekuensi pemberian intravena.

Instruksi cara pemberian dan penyiapannya
Injeksi Levetiracetam hanya untuk penggunaan intravena dan harus diencerkan dalam 100 mL pengencer yang kompatibel sebelum pemberian. Jika volume yang lebih kecil diperlukan, jumlah pengencer harus dihitung tidak melebihi konsentrasi Levetiracetam maksimum 15 mg per mL dari larutan yang diencerkan. Pertimbangan juga harus diberikan pada total asupan cairan harian pasien. Injeksi Levetiracetam harus diberikan sebagai infus IV 15 menit. Satu vial injeksi Levetiracetam mengandung 500 mg Levetiracetam (500 mg/5 mL).

Injeksi Levetiracetam dapat dicampur dengan pengencer berikut. Larutan yang dilarutkan stabil hingga 24 jam pada suhu kamar selama studi kompatibilitas dengan pengencer.
Pengencer :
- Sodium chloride 0.9%
- Injeksi Ringer laktat
- Injeksi Dekstrosa 5%

Produk obat parenteral harus diperiksa secara visual untuk partikel dan perubahan warna sebelum pemberian setiap kali di larutan & wadah yang tepat. Produk dengan adanya partikel atau perubahan warna tidak boleh digunakan.
Setiap bagian yang tidak terpakai dari isi vial injeksi Levetiracetam harus dibuang.

Dewasa
Lihat Tabel 1 untuk persiapan dan pemberian injeksi Levetiracetam yang direkomendasikan untuk orang dewasa untuk mencapai dosis 500 mg, 1000 mg, atau 1500 mg.

Tabel 1 : Persiapan dan Pemberian Injeksi Levetiracetam

Dosis	Volume yang diambil	Volume pelarut	Waktu infus
500 mg	5 mL (5 mL vial)	100 mL	15 menit
1000 mg	10 mL (dua 5 mL vial)	100 mL	15 menit
1500 mg	15 mL (tiga 5 mL vial)	100 mL	15 menit

Misalnya, untuk menyiapkan dosis 1000 mg, encerkan dengan 10 mL injeksi Levetiracetam dalam 100 mL pengencer yang kompatibel dan berikan secara intravena sebagai infus 15 menit.

Penyesuaian dosis pada pasien dewasa dengan gangguan ginjal
Pemberian Levetiracetam harus secara individual berdasarkan status fungsi ginjal pasien. Penyesuaian dosis yang direkomendasikan untuk dewasa dengan gangguan ginjal ditunjukkan pada Table 2. Informasi tidak tersedia untuk penyesuaian dosis pada pasien anak. Untuk menghitung dosis yang direkomendasikan untuk pasien dewasa dengan gangguan ginjal, bersihan kreatinin disesuaikan untuk area luas permukaan tubuh harus

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

dihitung. Untuk estimasi bersihan kreatinin pasien (CLcr) dalam mL/minute harus dihitung pertama kali dengan rumus :

$$CLcr = \frac{[140 - \text{usia (tahun)}] \times \text{berat (kg)}}{72 \times \text{serum kreatinin (mg/dL)}} \quad (\times 0.85 \text{ untuk pasien wanita})$$

Kemudian CLcr disesuaikan dengan luas permukaan tubuh (LPT) sebagai berikut :

$$CLcr\ (mL/menit/1.73m^2) = \frac{CLcr\ (mL/menit)}{\text{Subjek BSA } (m^2)} \times 1.73$$

Tabel 2 : Regimen penyesuaian dosis pada pasien dewasa dengan gangguan fungsi ginjal

Kelompok	**Bersihan kreatinin (mL/menit)**	**Dosis (mg)**	**Frekuensi**
Normal	> 80	500 hingga 1500	Setiap 12 jam
Ringan	50 – 79	500 hingga 1000	Setiap 12 jam
Sedang	30 – 49	250 hingga 750	Setiap 12 jam
Berat	< 30	250 hingga 500	Setiap 12 jam
Pasien ESRD yang menggunakan dialisis	----	500 hingga 1000	Setiap 24 jam[1]

[1] Setelah dialisis, direkomendasikan untuk penambahan dosis sebesar 250 hingga 500 mg

Penghentian Levetiracetam

Hindari penarikan tiba-tiba dari Levetiracetam untuk mengurangi risiko peningkatan frekuensi kejang dan status epileptikus.

Jika ada dosis LEVEXA yang terlewatkan,

- Dokter Anda akan menentukan waktu pemberian dosis **LEVEXA** selanjutnya untuk Anda. Anda perlu mendiskusikan hal ini dengan dokter Anda.

Jika Anda menghentikan pengobatan dengan LEVEXA

Pasien dan pengasuh yang merawat disarankan untuk tidak menghentikan penggunaan **LEVEXA** tanpa berkonsultasi dengan penyedia layanan kesehatan mereka. Levetiracetam biasanya harus ditarik secara bertahap untuk mengurangi potensi peningkatan frekuensi kejang dan status epileptikus. Mohon konsultasikan dengan dokter Anda jika penghentian cepat diperlukan jka pasien mengalami reaksi merugikan yang serius.

4. Efek samping yang mungkin terjadi

Seperti semua obat, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Jika Anda mengalami efek samping tertentu, sampaikan kepada dokter, apoteker, atau perawat Anda. Ini termasuk kemungkinan efek samping lainnya yang tidak tercantum dalam brosur ini.

Efek samping yang tercantum di bawah ini terjadi ketika **LEVEXA** diberikan. Hal ini tidak selalu berarti bahwa efek samping tersebut secara khusus disebabkan oleh **LEVEXA**.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Anda perlu langsung mencari pertolongan jika Anda mengalami salah satu dari efek samping berikut.

Efek samping berikut yang pernah dilaporkan
Reaksi obat yang merugikan (ADR) tercantum di bawah ini berdasarkan kelas organ sistem MedDRA berdasarkan frekuensi. Frekuensi didefinisikan sebagai :
Sangat umum >= 1/10;
Umum >= 1/100 hingga 1/10;
Tidak umum >= 1/1000 hingga =1/10000 hingga =1/1000

Infeksi dan infestasi
Sangat umum : Nasofaringitis
Jarang : Infeksi

Gangguan sistem darah dan limfatik
Tidak umum : Trombositopenia, leukopenia
Jarang : Pansitopenia, neutropenia, agranulositosis

Gangguan sistem kekebalan tubuh
Jarang : Reaksi obat dengan eosinofilia dan gejala sistemik/*Drug reaction with eosinophilia and systemic symptoms* (DRESS), hipersensitivitas (termasuk angioedema dan anafilaksis)

Gangguan metabolisme dan nutrisi
Umum : Anoreksia
Tidak umum : Penurunan berat badan menurun, peningkatan berat badan
Jarang : Hiponatremia

Gangguan kejiwaan
Umum : Depresi, permusuhan (*hostility*)/agresi, kecemasan, insomnia, gugup/mudah marah
Tidak umum : Percobaan bunuh diri, ide bunuh diri, gangguan psikotik, perilaku abnormal, halusinasi, kemarahan, keadaan bingung, serangan panik, memengaruhi labilitas/perubahan suasana hati, agitasi
Jarang : Keinginan bunuh diri, gangguan kepribadian, berpikir abnormal, delirium

Gangguan sistem saraf
Sangat umum : Somnolen, sakit kepala
Umum : Kejang, gangguan keseimbangan, pusing, letargi/lesu, tremor
Tidak umum : Amnesia, gangguan memori, gangguan koordinasi ataksia, parestesia, gangguan perhatian
Jarang : Koreoatetosis, diskinesia, hiperkinesia, gangguan gaya berjalan, ensefalopati, kejang diperparah

Gangguan mata
Tidak umum : Diplopia, penglihatan kabur

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Gangguan telinga dan labirin
Umum : Vertigo

Gangguan jantung
Jarang : Perpanjangan QT Elektrokardiogram

Gangguan pernapasan, toraks dan mediastinum
Umum : Batuk

Gangguan pencernaan
Umum : Sakit perut, diare, dispepsia, muntah, mual
Jarang : Pankreatitis

Gangguan hepatobilier
Tidak umum : Tes fungsi hati tidak normal
Jarang : Gagal hati, hepatitis

Gangguan ginjal dan saluran kemih
Jarang : Cedera ginjal akut

Gangguan kulit dan jaringan subkutan
Umum : Ruam
Tidak umum : Alopecia, eksim, pruritus
Jarang : Nekrolisis epidermal toksik, sindrom steven-johnson, eritema multiforme

Gangguan muskuloskeletal dan jaringan ikat
Tidak umum : Kelemahan otot, mialgia
Jarang : *Rhabdomyolysis* dan peningkatan kreatin fosfokinase darah*

Gangguan umum dan kondisi tempat pemberian
Umum : Astenia/kelelahan

Cedera, keracunan dan komplikasi prosedural
Tidak umum : Cedera
*prevalensi secara signifikan lebih tinggi pada pasien Jepang bila dibandingkan dengan pasien non-Jepang.

Deskripsi reaksi merugikan yang terpilih
Risiko anoreksia lebih tinggi ketika Levetiracetam diberikan bersama dengan Topiramate.
Dalam beberapa kasus alopecia, teramati adanya pemulihan ketika Levetiracetam dihentikan.
Supresi sumsum tulang diidentifikasi dalam beberapa kasus pansitopenia.
Kasus ensefalopati umumnya terjadi pada awal pengobatan (beberapa hari sampai beberapa bulan) dan bersifat reversibel setelah penghentian pengobatan.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

Bagaimana gejala dan penanganan jika menggunakan LEVEXA melebihi dosis yang seharusnya

Penanganan overdosis : Tidak ada obat penawar khusus untuk overdosis dengan Levetiracetam.

Hemodialisis : Prosedur hemodialisis standar menghasilkan pembersihan Levetiracetam yang signifikan (sekitar 50% dalam 4 jam) dan harus dipertimbangkan dalam kasus overdosis. Meskipun hemodialisis belum dilakukan pada beberapa kasus overdosis yang diketahui, hal ini dapat diindikasikan oleh keadaan klinis pasien atau pada pasien dengan gangguan ginjal yang signifikan.

Gejala dan tanda : Somnolen (rasa kantuk), agitasi, agresi, tingkat depresi/penurunan dari kesadaran, pernapasan dan depresi dan koma telah diamati dengan overdosis Levetiracetam.

Pelaporan efek samping

Apabila Anda mengalami efek samping apa pun, hubungi dokter, apoteker, atau perawat Anda. Hal ini termasuk semua efek samping lainnya yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi tambahan terkait keamanan obat ini.

Anda juga dapat melaporkan efek samping secara langsung melalui :

Pusat Farmakovogilans

c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif

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Faks: +62-21-4245523
Website: http://e-meso.pom.go.id/

5. Cara penyimpanan LEVEXA

- Jangan digunakan setelah tanggal kadaluarsa yang tertera pada dus.
- Simpan di bawah suhu 30ºC.
- Simpan dalam kemasan aslinya
- Jauhkan dari jangkauan dan penglihatan anak-anak
- Jangan menggunakan **LEVEXA** jika Anda menemukan partikel-partikel tertentu atau perubahan warna sebelum pemberian obat.
- Jangan membuang obat melalui saluran limbah cair atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak digunakan. Upaya-upaya ini akan membantu perlindungan lingkungan.

6. Isi kemasan dan informasi lainnya

Apa itu LEVEXA

- Bahan aktif dari **LEVEXA** adalah Levetiracetam.

DISETUJUI OLEH BPOM: 05/01/2023 EREG10042512100098

- Setiap vial (5 mL) mengandung Levetiracetam 500 mg
- Eksipien : Sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection.

Bentuk sediaan dan isi kemasan

LEVEXA merupakan larutan bening tidak berwarna, 5 mL vial kaca tubular tipe I yang disegel dengan *serum rubber stopper* warna abu-abu 20 mm dan segel aluminium *flip off* warna biru.

KEMASAN :
LEVEXA Injeksi 100 mg/mL
Dus, 1 vial @ 5 mL
No. Reg. …

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