Telox

(Oxcarbazepine)

Tablets 150, 300 & 600 mg

ٹی لوکس

(اوکسکاربازیپین)

Suspension 300 mg / 5 ml

COMPOSITION
Telox Tablets 150 mg
Each Film Coated Tablet contains:
Oxcarbazepine (U.S.P.) ..... 150 mg
Product Complies U.S.P. Specs

Telox Tablets 300 mg
Each Film Coated Tablet contains:
Oxcarbazepine (U.S.P.) ..... 300 mg
Product Complies U.S.P. Specs

Telox Tablets 600 mg
Each Film Coated Tablet contains:
Oxcarbazepine (U.S.P.) ..... 600 mg
Product Complies U.S.P. Specs

Telox Suspension 300 mg / 5 ml
Each 5 ml contains:
Oxcarbazepine (U.S.P.) ..... 300 mg
Product Complies U.S.P. Specs

DESCRIPTION
TELOX is an antiepileptic drug available as 150 mg, 300 mg and 600 mg Oxcarbazepine as film-coated tablets and suspension containing 300mg / 5 ml Oxcarbazepine for oral administration. Oxcarbazepine is 10,11-Dihydro-10-oxo-5H-dibenz [b, f] azepine-5-carboxamide.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Mechanism of Action
The pharmacological activity of Oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine .The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neuronal membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

Pharmacokinetics
Absorption
Following oral administration of Oxcarbazepine tablets; oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10 monohydroxy metabolite (MHD). The halt-life of the parent is about two hours, while the half-life of MHD is about nine hours, so that MHD is responsible for most antiepileptic activity.

After single-dose administration of Oxcarbazepine tablets to healthy male volunteers under fasted conditions, the median T_{max} was 4.5 (range 3 to 13) hours.

Effect of Food: Food has no effect on the rate and extent of absorption of oxcarbazepine from Oxcarbazepine tablets.

Distribution
The apparent volume of distribution of MHD is 49L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin, Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism and Excretion
Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolites, MHD, which is primarily responsible for the pharmacological effect of Oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10, 11- dihydroxy metabolite (DHD).

Oxcarbazepine is cleared from the body mostly in the form of metabolite which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose

Hepatic Impairment
The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900-mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for Oxcarbazepine is recommended in patients with mild-to-moderate hepatic Impairment. The pharmacokinetics of oxcarbazepine and MHD has not been evaluated in severe hepatic impairment.

Renal impairment
There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300-mg dose in renally Impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a two-fold increase in AUC. Dose adjustment for Oxcarbazepine is recommended in these patients.

Pediatric Use
After a single-dose administration of 5 or 15 mg/kg of oxcarbazepine, the dose-adjusted AUC values of MHD were 30%-40% lower in children below the age of eight years than in children above eight years of age. The clearance in children greater than eight years old approaches that of adults.

Geriatric Use
Following administration of single (300 mg) and multiple (600 mg/day) doses of Oxcarbazepine to elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30%-60% higher than in younger volunteers (18-32 years of age). Comparison of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

INDICATIONS
TELOX is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4 - 16 with epilepsy.

CONTRAINDICATIONS
TELOX should not be used in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

SIDE EFFECTS
Most Common Adverse Events in All Clinical Studies
Adjunctive Therapy/Mono therapy in Adults Previously Treated with other AEDs:
The most commonly observed (•5%) adverse experiences seen in association with oxcarbazepine were: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia; abnormal gait.

Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with other AEDs: The most commonly observed (•5%) adverse experiences seen in association with Oxcarbazepine in these patients were similar to those seen in adults.

Monotherapy in Adults not Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with Oxcarbazepine in these patients were similar to those in adults previously treated patients.

Monotherapy in Pediatric Patients not previously treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with Oxcarbazepine in these patients were similar to those in adults.
Other events.
observed in association with the administration of oxcarbazepine.

Body as a Whole: Fever, malaise, pain chest precordial, rigors, weight decrease.

Cardiovascular System: Bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: Appetite increased, blood in stool, cholelithiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, dry mouth, biliary pain, right hypochondrium pain, retching, sialoadenitis, stomatitis, stomatitis ulcerative.

Hemic and Lymphatic System: Leukopenia, thrombocytopenia.

Laboratory Abnormality: Gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: Hypertonia muscle.

Nervous System: Aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extrapyramidal disorder, feeling drunk, hemiplegia, hyperkinesia, hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychosis, ptosis, stupor, tetany.

Respiratory System: Asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Urogenital and Reproductive System: Dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, renal pain, urinary tract pain, polyuria, priapism, renal calculus.

Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

DRUG ABUSE AND DEPENDENCE
Abuse
The abuse potential of Oxcarbazepine has not been evaluated in human studies.

Dependence
Intragastric injections of oxcarbazepine to four cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to salt-administer oxcarbazepine by levir pressing activity.

WARNINGS
Hyponatremia
Clinically significant hyponatremia (sodium <125 mmol/L) can develop during TELOX use.

Measurement of serum sodium levels should be considered for patients during maintenance treatment with Oxcarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels (for example, drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (e.g., nausea, malaise, headache, lethargy. confusion, obtundation, or increase in seizure frequency or severity).

Withdrawal of AEDs
As with all antiepileptic drugs, Oxcarbazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS
Cognitive/Neuropsychiatric Adverse Events
Use of Oxcarbazepine has been associated with central nervous system-related adverse events. The most significant of these can be clssaified into three general categories: 1) cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems, 2) somnolence or fatigue, and 3) coordination abnormalities, including ataxia and gait disturbances.

Pregnancy Category C

There are no adequate and well-controlled clinical studies of Oxcarbazepine in pregnant women; however, Oxcanbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans, Given this fact, and the results of the animal studies described, it is likely that Oxcarbazepine is a human teratogen, TELOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of Oxcarbazepine on labor and delivery in humans has not been evaluated.

Nursing Mothers
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to Oxcarbazepine in nursing infants, to decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

Patients with Renal Impairment
In renally-impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged with a corresponding two-fold increase in AUC.

Pediatric Use
TELOX is indicated for use as adjunctive therapy or monotherapy for partial seizures in patients aged 4-16 years old.

DRUG INTERACTIONS
Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

Antiepileptic Drugs
Potential interactions between Oxcarbazepine and other AEDe were assessed in clinical studies, The effect of these interactions on mean AUCs and Cmin are summarized.

Table 1: Summary of AED Interactions with Oxcarbazepine

AED Coadministered	Dose of AED (mg/day)	Oxcarbazepine Dose (mg/day)	Influence of Oxcarbazepine on AEDconcentration (Mean Change, 90% Confidence Interval)	Influence of of AED on MHD Concentration (Mean Change, 90% Confidence Interval)
Carbamazepine	400-2000	900	nc[1]	40% decrease [CI:17% decrease 57% decrease]
Phenobarbital	100-150	600-1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI:12% decrease 51% decrease]
Phenytoin	250-500	600-1800 >1200-2400	nc1,2 up to 40% increase[3] [CI:12% increase, 60% increase]	30% decrease [CI:3% decrease 48% decrease]
Volproic acid	400-2800	600-1800	nc[1]	18% decrease [CI:13% decrease 40% decrease

1. nc denotes a mean change of less than 10%
2. Pediatrics
3. Mean increase in adults at high Oxcarbazepine doses

Hormonal Contraceptives
Coadministration of Oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of the two - hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22- 65] in one study and 52% [90% CI: 38-52) in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20-45] in one study and 52% [90% CI: 42-52] in another study. Therefore. concurrent use of Oxcarbazepine with hormonal contraceptives may render these contraceptives less effective. Studies with other oral or implant contraceptives have not been conducted.

Calcium Antagonists
After repeated coadministration of Oxcarbazepine, the AUC of felodipine was lowered by 28% [90% CI: 20-33].

Verapamil produced a decrease of 20% [90% CI:18-27] of the plasma levels of MHD.

Other Drug Interactions
Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD. Results with warfarin show no evidence of Interaction with either single or repeated doses of oxcarbazepine.

DOSAGE AND ADMINISTRATION
TELOX is recommended as adjunctive treatment and monotherapy in the treatment of partial seizures in adults and children ages 4-16. All dosing should be given in a twice-a-day (BID) regimen. TELOX should be kept out of the reach and sight of children.

Adults
Adjunctive Therapy
Treatment with TTELOX should be initiated with a dose of 600 mg/day, given in a BID regimen. If clinically indicated, the dose may be Increased by a maximum of 600 mg/day at approximately weekly intervals; the recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant AEDs be monitored during the period of TELOX titration, as these plasma levels may be altered, especially at TELOX doses greater than 1200 mg/day.

Conversion to Monotherapy
Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with TELOX at 600 mg/day (given in a BID regimen) while simultaneously initiating the reduction of the dose of the concomitant AEDs. The concomitant AEDs should be completely withdrawn over 3-6 weeks, while the maximum dose of Telox should be reached in about 2-4 weeks. TELOX may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the - recommended daily dose of 2400 mg/day, A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been initiated with Telox. Patients should be observed closely during this transition phase.

Initiation of Monotherapy
Patients not currently being treated with AEDs may have monotherapy - initiated with TELOX. In these patients, TELOX should be initiated at a dose of 600 mg/day (given in a BID regimen); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown lobe effective in patients converted from other AEDs to TELOX monotherapy.

Pediatric Patients Age 4-16
Adjunctive Therapy
Treatment should be initiated at a daily dose of 8-10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The target maintenance dose of TELOX should be achieved over two weeks, and is dependent upon patient weight, according to the following chart.

20 - 29 kg - 900 mg/day
29.1-39 kg -1200 mg/day
>39 kg -1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6-51 mg/kg.

The pharmacokinetic of Oxcarbazepine are similar in older children (age >8 yrs) and adults. However, younger children (age <8 yrs) have an increased clearance (by about 30%-40%) compared with older children and adults. In the controlled trial, pediatric patients eight years old and below received the highest maintenance doses.

Conversion to Monotherapy
Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with TELOX at approximately 8-10 mg/kg/day given in a BID regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3-6 weeks while TELOX may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

Initiation of Monotherapy
Patient not currently being treated with antiepileptic drugs may have monotherapy initiated with Oxcarbazepine In these patients, TELOX should be initiated at a dose of 8-10 mg/kg/day given in a BID regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in the table below.

Table: Range of Maintenance Doses of Oxcarbazepine for children by weight During Monotherapy

	From	To
Weight in kg	Dose (mg/day)	Dose (mg/day)
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

Patients with Hepatic Impairment
In general, dose adjustments are not required in patients with mild-to-moderate hepatic impairment.

Patients with Renal Impairment
In patients with impaired renal function (creatine clearance <30 mL/min) Oxcarbazepine therapy should be initiated at one-half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response.

OVERDOSAGE
Human Overdose Experience
Isolated cases of overdose with oxcarbazepine have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment.

Treatment and Management
There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

HOW SUPPLIED
Telox Tablets 150 mg: Film Coated Tablets: blister pack of 5 x 10's
Telox Tablets 300 mg: Film Coated Tablets: blister pack of 5 x 10's
Telox Tablets 600 mg: Film Coated Tablets: blister pack of 5 x 10's
Telox Oral Suspension 300 mg / 5 ml: 60 ml in bottle
Telox Oral Suspension 300 mg / 5 ml: 120 ml in bottle

STORAGE:
Store below 30°C in a dry place. Protect from light.
Keep out of the reach of children.
To be dispensed only on the prescription of a registered medical practitioner only.

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
صرف مستند معالج کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

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