NOVARTIS

Oxcarbazepine

Trileptal®

60 mg/mL Oral Suspension.

Antiepileptic (Carboxamide derivative)

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Off-white to slightly reddish brown oral suspension.

Active substance

1 mL of the oral suspension contains 60 mg oxcarbazepine.

Excipients

Propyl parahydroxybenzoate (E 216); saccharin sodium; sorbic acid (E 200); macrogol stearate 400; methyl parahydroxybenzoate (E 218); yellow-plum-lemon flavor; ascorbic acid (E 300); dispersible cellulose; propylene glycol; sorbitol 70% (non-crystallising); water purified.

Ethanol is a component of the flavor.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Indicated in adults and in children aged 1 month and above for the treatment of

- Partial seizures (which include the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures) and
- Generalized tonic-clonic seizures.

It is indicated as a first-line antiepileptic drug for use as monotherapy or adjunctive therapy.

It can replace other antiepileptic drugs when current therapy provides insufficient seizure control (see section CLINICAL STUDIES).

DOSAGE AND ADMINISTRATION

Dosage

Oxcarbazepine (Trileptal®) is suitable for use either as monotherapy or in combination with other antiepileptic drugs. In mono- and adjunctive therapy, treatment is initiated with a clinically effective dose given in two divided doses (see section CLINICAL STUDIES). The dose may be increased depending on the clinical response of the patient.

When used as replacement for other antiepileptic drugs, the dose of the concomitant antiepileptic drug(s) should be reduced gradually on initiation of therapy. In adjunctive therapy, as the total antiepileptic drug load of the patient is increased, the dose of concomitant antiepileptic drug(s) may need to be reduced and/or the dose increased more slowly (see section INTERACTIONS).

Oxcarbazepine (Trileptal®) oral suspension and film-coated tablets are bioequivalent and may be interchanged at equal doses (see section CLINICAL PHARMACOLOGY).

The prescription for oxcarbazepine (Trileptal®) oral suspension should be given in milliliters (see conversion table 1 below which gives the milligram dose in milliliters).

Table 1 Dosage in milligrams vs. milliliters

Dose in milligrams (mg)	**Dose in milliliters (mL)**
10 mg	0.2 mL
20 mg	0.3 mL
30 mg	**0.5 mL**
40 mg	0.7 mL
50 mg	0.8 mL
60 mg	**1.0 mL**
70 mg	1.2 mL
80 mg	1.3 mL
90 mg	**1.5 mL**
100 mg	1.7 mL
200 mg	3.3 mL
300 mg	**5.0 mL**
400 mg	6.7 mL
500 mg	8.3 mL
600 mg	**10.0 mL**
700 mg	11.7 mL
800 mg	13.3 mL
900 mg	**15.0 mL**
1,000 mg	16.7 mL

Therapeutic drug monitoring

The therapeutic effect of oxcarbazepine is primarily exerted through the active metabolite 10-monohydroxy derivative (MHD) of oxcarbazepine (section CLINICAL PHARMACOLOGY).

Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted. However, plasma level monitoring of MHD may be considered during therapy in order to rule out noncompliance, or in situations where an alteration in MHD clearance is to be expected, including:

- changes in renal function (see section Dosage in renal impairment)
- pregnancy (see Section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL and section CLINICAL PHARMACOLOGY)
- concomitant use of liver enzyme-inducing drugs (see section INTERACTIONS)

If any of these situations apply, the dose may be adjusted (based on plasma levels measured 2-4 hours post dose) to maintain peak MHD plasma levels < 35 mg/L.

General target population

Adults

Monotherapy and adjunctive therapy

Recommended initial dose

Treatment should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses.

Maintenance dose

Good therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals from the starting dose to achieve the desired clinical response.

Maximum recommended dose

In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.

Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

There is only limited experience with doses up to 4,200 mg/day.

Special populations

Pediatric patients

Recommended initial dose

In mono- and adjunctive therapy, treatment should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses.

Maintenance dose

The target maintenance dose for adjunctive therapy is 30-46 mg/kg/day and should be achieved over two weeks.

In an adjunctive therapy trial in pediatric patients (aged 3 to 17 years), in which the intention was to reach a target daily dose of 46 mg/kg/day, the median daily dose was 31 mg/kg/day with a range of 6 to 51 mg/kg/day.

In an adjunctive therapy trial in pediatric patients (aged 1 month to less than 4 years), in which the intention was to reach a target daily dose of 60 mg/kg/day, 56% of patients reached a final dose of at least 55 mg/kg/day.

Maximum recommended dose

If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day at approximately weekly intervals from the starting dose, to a maximum daily dose of 60 mg/kg/day, to achieve the desired clinical response (see section CLINICAL PHARMACOLOGY).

Effect of weight adjusted MHD clearance on pediatric dosage

Under adjunctive therapy and monotherapy, when normalized by body weight, apparent clearance (L/hr/kg) of MHD (the active metabolite of oxcarbazepine) decreased with age such that children 1 month to less than 4 years of age may require twice the oxcarbazepine dose per body weight compared to adults; and children 4 to 12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults (see section CLINICAL PHARMACOLOGY).

Effect of concomitant enzyme-inducing antiepileptic drugs on pediatric dosage

For children 1 month to less than 4 years of age, the influence of enzyme-inducing antiepileptic drugs on weight-normalized apparent clearance appeared higher compared to older children. For children 1 month to less than 4 years of age, an approximately 60% higher oxcarbazepine dose per body weight may be required for adjunctive therapy on enzyme-inducing antiepileptic drugs compared to monotherapy or adjunctive therapy with non-enzyme-inducing antiepileptic drugs. For older children on enzyme-inducing antiepileptic drugs, only a slightly higher dose per body weight may be required than their counterparts on monotherapy.

Oxcarbazepine (Trileptal®) has not been studied in controlled clinical trials in children below 1 month of age.

Geriatric patients (65 years old and above)

No special dose recommendations are necessary in elderly patients because therapeutic doses are individually adjusted. Dosage adjustments are recommended in elderly patients with renal impairment (creatinine clearance <30 ml/min) (see information below on dosage in renal impairment).

Close monitoring of sodium levels is required in patients at risk of hyponatremia (see section WARNINGS AND PRECAUTIONS).

Hepatic impairment

No dosage adjustment is required for patients with mild to moderate hepatic impairment. Oxcarbazepine (Trileptal®) has not been studied in patients with severe hepatic impairment, therefore, caution should be exercised when dosing such patients (see section CLINICAL PHARMACOLOGY and section WARNINGS AND PRECAUTIONS).

Renal impairment

In patients with impaired renal function (creatinine clearance less than 30 mL/min), therapy should be initiated at half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see section CLINICAL PHARMACOLOGY and section WARNINGS AND PRECAUTIONS).

Method of administration

Oxcarbazepine (Trileptal®) can be taken with or without food (see section CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Known hypersensitivity to oxcarbazepine or eslicarbazepine or to any of the excipients of oxcarbazepine (Trileptal®).

WARNINGS AND PRECAUTIONS

Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine (Trileptal®). If a patient develops these reactions after treatment, the drug should be discontinued and an alternative treatment started.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions (see section ADVERSE DRUG REACTIONS).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section ADVERSE DRUG REACTIONS). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, therapy should be withdrawn immediately.

Dermatological effects

Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with the use of oxcarbazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Oxcarbazepine-associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when re-challenged were reported. Should a patient develop a skin reaction, consideration should be given to discontinuing treatment and prescribing another anti-epileptic drug.

Pharmacogenomics

There is growing evidence that different Human Leukocyte Antigen (HLA) alleles play a role in association with adverse cutaneous reactions in predisposed patients.

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. As the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the HLA-B*1502 allele also have an increased risk of SJS/TEN skin reactions with oxcarbazepine.

The frequency of HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations and is about 8% in Thai populations, and above 15% in the Philippines and some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%).

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e., the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations prior to initiating treatment with treatment (see below Information for healthcare professionals). Use should be avoided in tested patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoid use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low or in current users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

Association with HLA-A*3101

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population. The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations with some exceptions within 5 to 12%. Frequency above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10% to 15% in other native ethnicities in these same regions.

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e., the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

There is some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine-induced cutaneous adverse drug reactions including SJS, TEN, drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash.

There are insufficient data to support a recommendation for testing the presence of the HLA-A*3101 allele in patients prior to initiating treatment with oxcarbazepine. Genetic screening is generally not recommended for any current users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

Limitation of genetic screening

Genetic screening results must never substitute appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with oxcarbazepine will not develop SJS/TEN, and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. Similarly, many patients positive for HLA-A*3101 will not develop SJS, TEN, DRESS, AGEP or maculopapular rash, and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for healthcare professionals

If testing for the presence of the HLA-B*1502 allele is performed, high-resolution “HLA-B*1502 genotyping” is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected, and negative if no HLA-B*1502 alleles are detected. Similarly, if testing for the presence of the HLA-A*3101 allele is performed, high resolution “HLA-A*3101 genotyping” is recommended. The test is positive if either one or two HLA- A*3101 alleles are detected, and negative if no HLA-A*3101 alleles are detected.

Risk of seizure aggravation

Risk of seizure aggravation has been reported. The risk of seizure aggravation is seen especially in children but may also occur in adults. In case of seizure aggravation, treatment should be discontinued.

Hyponatremia

Serum sodium levels below 125 mmol/L, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2.7% of treated patients. Experience from clinical trials shows that serum sodium levels returned towards normal when the oxcarbazepine dosage was reduced, discontinued or the patient was treated conservatively (e.g. restricted fluid intake).

In patients with pre-existing renal conditions associated with low sodium levels (e.g. inappropriate ADH secretion like syndrome) or in patients treated concomitantly with sodium-lowering drugs (e.g. diuretics, drugs associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients.

For patients on oxcarbazepine therapy when starting on sodium-lowering drugs, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on therapy (see section ADVERSE DRUG REACTIONS), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium levels should be checked. If hyponatraemia is observed, water restriction is an important counter-measure. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV-block, arrhythmia) should be monitored carefully.

Hypothyroidism

Hypothyroidism is a very rare adverse drug reaction of oxcarbazepine. Considering the importance of thyroid hormones in children's development after birth, it is advisable to perform a thyroid function test before the start of therapy in the pediatric age group, especially in children aged two years or below. Thyroid function monitoring is recommended in the pediatric age group while on therapy.

Hepatic function

Very rare cases of hepatitis have been reported, which in most cases resolved favorably. In case of suspected hepatitis, discontinuation of treatment should be considered. Caution should be exercised when treating patients with severe hepatic impairment (see sections DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Renal function

In patients with impaired renal function (creatinine clearance less than 30 mL/min), caution should be exercised during treatment especially with regard to the starting dose and up titration of the dose (see sections DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Hematological effects

Very rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in treated patients during post-marketing experience (see section ADVERSE DRUG REACTIONS). However, due to the very low incidence of these conditions and confounding factors (e.g. underlying disease, concomitant medication), causality cannot be established.

Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Suicidal ideation and behavior

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic drugs has shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known.

Therefore patients should be monitored for signs of suicidal ideation and behavior, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Interactions

Hormonal contraceptives: Female patients of childbearing age should be warned that the concurrent use of oxcarbazepine (Trileptal®) with hormonal contraceptives may render this type of contraception ineffective (see sections INTERACTIONS and PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL). Additional, non-hormonal forms of contraception are recommended when using oxcarbazepine.

Alcohol

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.

Withdrawal effects

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

Driving and using machines

Adverse reactions, such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatremia and depressed level of consciousness were reported (for the complete list of ADRs see section ADVERSE DRUG REACTIONS), especially at the start of treatment or in connection with dose adjustments (more frequently during the up titration phase). Patients should therefore exercise due caution when driving a vehicle or operating machinery.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.

In clinical trials, adverse events (AEs) were generally mild to moderate in severity, of transient nature and occurred predominantly at the start of treatment.

The analysis of the undesirable effect profile by body system is based on AEs from clinical trials assessed as related to oxcarbazepine. In addition, clinically meaningful reports on adverse experiences from named patient programs and post-marketing experience were taken into account.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Adverse drug reactions

Blood and lymphatic system disorders	
Uncommon	Leucopenia.
Very rare	Bone marrow depression, aplastic anemia, agranulocytosis, pancytopenia, thrombocytopenia, neutropenia.
Immune system disorders	
Very rare	Anaphylactic reactions, hypersensitivity (including multi-organ hypersensitivity) characterized by features such as rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly), liver (e.g. hepatitis, abnormal liver function tests), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidneys (e.g. renal failure, nephritis interstitial, proteinuria), lungs (e.g. pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnea), angioedema.
Endocrine disorders	
Common	Weight increased
Very rare	Hypothyroidism
Metabolism and nutrition disorders	
Common	Hyponatraemia.
Very rare	Hyponatraemia* associated with signs and symptoms such as seizures, encephalopathy, depressed level of consciousness, confusion (see also Nervous system disorders for further adverse effects), vision disorders (e.g. blurred vision), hypothyroidism, vomiting, nausea, folic acid deficiency.
Psychiatric disorders	
Common	Agitation (e.g. nervousness), affect lability, confusional state, depression, apathy.
Nervous system disorders	
Very common	Somnolence, headache, dizziness.
Common	Ataxia, tremor, nystagmus, disturbance in attention, amnesia.
Eye disorders	
Very common	Diplopia.
Common	Vision blurred, visual disturbance.
Ear and labyrinth disorders	
Common	Vertigo.
Cardiac disorders	
Very rare	Atrioventricular block, arrhythmia.
Vascular disorders	
Very rare	Hypertension.
Gastrointestinal disorders	
Very common	Vomiting, nausea.
Common	Diarrhoea, abdominal pain, constipation.
Very rare	Pancreatitis and/or lipase and/or amylase increase.

Hepatobiliary disorders	
Very rare	Hepatitis.
Skin and subcutaneous tissue disorders	
Common	Rash, alopecia, acne.
Uncommon	Urticaria.
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, erythema multiforme.
Musculoskeletal, connective tissue and bone disorders	
Very rare	Systemic lupus erythematosus.
General disorders and administration site conditions	
Very common	Fatigue.
Common	Asthenia.
Investigations	
Uncommon	Hepatic enzymes increased, blood alkaline phosphatase increased.
Very rare	Amylase increase, lipase increase

*Very rarely, clinically significant hyponatraemia (sodium < 125 mmol/L) can develop during use. It generally occurred during the first 3 months of treatment, although there were patients who first developed serum sodium < 125 mmol/L more than 1 year after initiation of therapy (see section WARNINGS AND PRECAUTIONS).

In clinical trials in children aged 1 month to less than 4 years, the most commonly reported adverse reaction was somnolence occurring in approximately 11% of patients. Adverse reactions occurring at an incidence of ≥ 1% - < 10% (common) were: ataxia, irritability, vomiting, lethargy, fatigue, nystagmus, tremor, decreased appetite, and blood uric acid increased.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with oxcarbazepine (Trileptal®) via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

Inappropriate ADH secretion like syndrome with signs and symptoms of lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms.

Skin and subcutaneous tissue disorders

Drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP).

Injury, poisoning and procedural complications

Fall.

Nervous system disorders

Speech disorders (including dysarthria); more frequent during up titration of oxcarbazepine (Trileptal®) dose.

Musculoskeletal, connective tissue and bone disorders

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with oxcarbazepine. The mechanism by which oxcarbazepine affects bone metabolism has not been identified.

INTERACTIONS

Enzyme inhibition

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. The results demonstrate that

oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses with drugs that are metabolized by CYP2C19 (e.g. phenobarbital, phenytoin, see below). In some patients treated with oxcarbazepine and drugs metabolized via CYP2C19 dose reduction of the co-administered drugs might be necessary. In human liver microsomes, oxcarbazepine and MHD have little or no capacity to function as inhibitors for the following enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11.

Enzyme induction

Oxcarbazepine and MHD induce, *in vitro* and *in vivo*, cytochromes CYP3A4 and CYP3A5 responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives, and antiepileptic drugs (e.g. carbamazepine), resulting in a lower plasma concentration of these drugs (see below). A decrease in plasma concentrations may also be observed for other drugs mainly metabolized by CYP3A4 and CYP3A5, for example immunosuppressants (e.g. ciclosporin).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferase. Therefore, *in vivo* they are unlikely to have an effect on drugs which are mainly eliminated by conjugation through the UDP-glucuronyl transferases (e.g. valproic acid, lamotrigine). Even in view of the weak induction potential of oxcarbazepine and MHD, a higher dose of concomitantly used drugs which are metabolized via CYP3A4 or via conjugation (UDPGT) may be necessary. In the case of discontinuation of oxcarbazepine (Trileptal®) therapy, a dose reduction of the concomitant medication may be necessary.

Induction studies conducted with human hepatocytes confirmed oxcarbazepine and MHD as weak inducers of isoenzymes of the 2B and 3A4 CYP sub-family. The induction potential of oxcarbazepine/MHD on other CYP isoenzymes is not known.

Antiepileptic drugs and enzyme inducing drugs

Potential interactions between oxcarbazepine and other antiepileptic drugs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in the following table 3.

Table 3 Summary of antiepileptic drug interactions with oxcarbazepine (Trileptal®)

Antiepileptic drug	**Influence of Oxcarbazepine on antiepileptic drug**	**Influence of antiepileptic drug on MHD**
Co-administered	Concentration	Concentration
Carbamazepine	0 - 22 % decrease	40 % decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Phenobarbital	14 - 15 % increase	30 - 31 % decrease
Phenytoin	0 - 40 % increase	29 - 35 % decrease
Valproic acid	No influence	0 - 18 % decrease
Lamotrigine	No influence	No influence

In vivo, plasma levels of phenytoin increased by up to 40% when oxcarbazepine was given at doses above 1,200 mg/day. Therefore, when using doses greater than 1,200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required (see section DOSAGE AND ADMINISTRATION). The increase in the phenobarbital level, however, is small (15%) when given with oxcarbazepine.

Strong inducers of cytochrome P450 enzymes and/or UGT (e.g. rifampicin, carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29-49%).

No autoinduction has been observed with oxcarbazepine.

Hormonal contraceptives

Oxcarbazepine was shown to have an influence on the two components, ethinylestradiol (EE) and levonorgestrel (LNG), of an oral contraceptive. The mean AUC values of EE and LNG were decreased by 48-52% and 32-52%, respectively. Studies with other oral or implant contraceptives have not been conducted. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives ineffective (see sections WARNINGS AND PRECAUTIONS and PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Calcium antagonists

After repeated co-administration of oxcarbazepine, the AUC values of felodipine were lowered by 28%. However, the plasma levels remained in the recommended therapeutic range.

On the other hand, verapamil produced a decrease of 20% in the plasma levels of MHD. This decrease in MHD plasma levels is not considered to be of clinical relevance.

Other drug interactions

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, whereas viloxazine produced minor changes in the MHD plasma levels (about 10% higher after repeated co-administration). Results with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations.. Most frequently observed congenital malformations with the use of oxcarbazepine were ventricular septal defect, atrioventricular septal defect, cleft palate with cleft lip, Down's syndrome, dysplastic hip (both unilateral and bilateral), tuberous sclerosis and congenital malformation of the ear.

Based on data in a North American pregnancy registry and EURAP registry (European and International Registry of Antiepileptic Drugs and Pregnancy), the prevalence of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 2.2% (95% CI 0.6 to 5.5% and assessed after 1 year of birth was 3.0% (95% CI: 1.4 to 5.4) respectively, among mothers exposed to oxcarbazepine monotherapy in the first trimester. When compared with pregnant women not exposed to any antiepileptic drugs the relative risk (RR) of congenital abnormality in pregnant women on oxcarbazepine is (RR) 1.6, 95% CI 0.46 to 5.7. Data on epileptic pregnant women receiving oxcarbazepine and unborn child exposed to oxcarbazepine during pregnancy remain inconclusive. However, risk of potential teratogenicity and neurodevelopmental disorders cannot be completely excluded.

Clinical considerations

Taking these data into consideration:

- If women receiving oxcarbazepine become pregnant, or plan to become pregnant, or if the need to initiate treatment, arises during pregnancy, the drug's potential benefits must be carefully weighed against the potential risk of fetal malformations. This is particularly important during the first three months of pregnancy.
- Minimum effective doses should be given.
- In women of childbearing age, whenever possible, it is recommended that oxcarbazepine should be administered as monotherapy. The potential for congenital abnormalities in the offspring of women treated with combination therapies is greater than those receiving monotherapy.
- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

- During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

Monitoring and prevention

Antiepileptic drugs may contribute to folic acid deficiency, a possible contributory cause of fetal abnormality. Folic acid supplementation is recommended before and during pregnancy.

Due to physiological changes during pregnancy, plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. It is recommended that clinical response should be monitored carefully in women receiving treatment during pregnancy and determination of changes in MHD plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy (see section DOSAGE AND ADMINISTRATION and section CLINICAL PHARMACOLOGY). Postpartum MHD plasma levels may also be considered for monitoring especially in the event that medication was increased during pregnancy.

In the newborn child

Bleeding disorders in the newborn caused by antiepileptic agents have been reported. As a precaution, vitamin K_1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.

Oxcarbazepine and its active metabolite (MHD) cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

Animal data

Standard reproductive toxicity studies in rodents and rabbits revealed effects such as increases in the incidence of embryo-fetal mortality and/or some delay in antenatal and/or postnatal growth of the offspring at maternally toxic dose levels. There was an increase in rat fetal malformations in one of the eight embryo-fetal toxicity studies, which were conducted with either oxcarbazepine or MHD, at doses which also caused maternal toxicity. The overall evidence from all animal studies indicates that oxcarbazepine has minor teratogenic potential at doses relevant to humans. However, the animal studies were insufficient to rule out a teratogenic effect of oxcarbazepine.

Lactation

Risk summary

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. Limited data indicate that the breastfed infants' MHD plasma concentrations correspond to up to 5% of the maternal MHD plasma concentration. Although exposure appears to be low, a risk to the infant cannot be excluded. Therefore, a decision whether to continue breastfeeding while using oxcarbazepine should be considered based on the benefit of breastfeeding and the potential risk of side effects in the infant. If breastfed, the infant should be monitored for adverse effects such as drowsiness and poor weight gain.

Females and males of reproductive potential

Contraception

Women of child bearing potential should be advised to use highly effective contraception (preferably non-hormonal; e.g. intrauterine implants) while on treatment. Oxcarbazepine (Trileptal®) may result in a failure of the therapeutic effect of hormonal contraceptive drugs containing ethinylestradiol (EE) and levonorgestrel (LNG) (see sections WARNING AND PRECAUTIONS and INTERACTIONS).

Infertility

There are no human data on fertility.

In rats, fertility in both sexes was unaffected by oxcarbazepine or MHD at oral doses up to 150 and 450 mg/kg/day, respectively. However, disruption of estrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals at the highest dose of MHD.

OVERDOSAGE

Isolated cases of overdose have been reported. The maximum dose taken was approximately 48,000 mg.

Signs and symptoms

Electrolyte and fluid balance conditions: hyponatremia

Eye disorders: diplopia, miosis, blurred vision

Gastrointestinal disorders: nausea, vomiting, hyperkinesia

General disorders and administration site conditions: fatigue

Investigations: respiratory rate depression, QTc prolongation

Nervous system disorders: drowsiness and somnolence, dizziness, ataxia, nystagmus, tremor, disturbances in coordination (coordination abnormal), convulsion, headache, coma, loss of consciousness, dyskinesia

Psychiatric disorders: aggression, agitation, confusional state

Vascular disorders: hypotension

Respiratory, thoracic and mediastinal disorders: dyspnoea

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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (MHD) of oxcarbazepine (see Pharmacokinetics (PK) – Biotransformation/ Metabolism). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects. No significant interactions with brain neurotransmitter or modulator receptor sites were found.

Pharmacodynamics (PD)

Oxcarbazepine and its active metabolite (MHD), are potent and efficacious anticonvulsants in animals. They protected rodents against generalized tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminum implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

Pharmacokinetics (PK)

Absorption

Following oral administration of oxcarbazepine (Trileptal®) tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active metabolite (10-monohydroxy derivative, MHD).

After single dose administration of 600 mg oral suspension to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 24.9 micromol/L, with a corresponding median t_{max} of 6 hours.

The tablet and suspension formulations of oxcarbazepine are bioequivalent since the geometric mean ratio (90% confidence interval) of single dose and steady state C_{max} and AUC of MHD were in the range 0.85 to 1.06.

In a mass balance study in man, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70% was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.

Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, it can be taken with or without food (see section DOSAGE AND ADMINISTRATION).

Distribution

The apparent volume of distribution of MHD is 49 liters.

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

Biotransformation/Metabolism

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

Elimination

Oxcarbazepine is cleared from the body mostly in the form of metabolites, 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%), whereas the inactive DHD accounts for approximately 3% and conjugates of oxcarbazepine account for 13% of the dose.
Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast, the apparent plasma half-life of MHD averaged 9.3 ± 1.8 h.

Linearity/non-linearity

Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when oxcarbazepine (Trileptal®) is given twice a day. At steady-state, the pharmacokinetics of MHD are linear and show dose proportionality across the dose range of 300 to 2,400 mg/day.

Special populations

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. Oxcarbazepine (Trileptal®) has not been studied in patients with severe hepatic impairment.

Renal impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When administered as a single 300 mg dose in renally impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged by up to 19 hours, with a two fold increase in AUC.

Pediatric patients (below 18 years)

Weight-adjusted MHD clearance decreases as age and weight increases approaching that of adults. The mean weight-adjusted clearance in children 1 month to less than 4 years of age is 93% higher than that of adults. Therefore, MHD exposure in these children is expected to be about one-half that of adults when treated with a similar weight-adjusted dose. The mean weight-adjusted clearance in children 4 to 12 years of age is 43% higher than that of adults. Therefore, MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight-adjusted MHD clearance is expected to reach that of adults.

Pregnancy

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy (see section DOSAGE AND ADMINISTRATION and section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Geriatric patients (65 years or above)

Following administration of single (300 mg) and multiple doses (600 mg/day) in elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30 to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

Gender

No gender related pharmacokinetic differences have been observed in children, adults, or the elderly.

CLINICAL STUDIES

A total of 10 double blind, well controlled trials, 2 in adjunctive therapy and 8 in monotherapy were conducted in patients with partial seizures which included the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures. All comparative trials also included patients with generalized tonic-clonic seizures.

Two dose-control monotherapy substitution trials in which patients received a variety of concomitant antiepileptic drugs which included carbamazepine, gabapentin, lamotrigine, phenytoin, and valproate confirm efficacy when these antiepileptic drugs were substituted by oxcarbazepine. Two trials were conducted in children (aged 3 to 17 years), one in adjunctive therapy versus placebo, the other a monotherapy comparison with phenytoin.

Efficacy was demonstrated with doses ranging from 600 mg/day to 2,400 mg/day in all the primary efficacy parameters which included mean or percentage change in seizure frequency from baseline in the adjunctive trials and time to meeting pre-defined exit criteria or the percentage of patients meeting exit criteria in the monotherapy trials.

An adjunctive therapy, rater-blind, trial in children (aged 1 month to less than 4 years) with inadequately-controlled partial seizures on one to two concomitant antiepileptic drugs was conducted, comparing two doses of oxcarbazepine. The primary measure of effectiveness was a between group comparison of the absolute

change in study specific seizure frequency per 24 hours compared to the seizure frequency at baseline. This comparison was statistically significant in favor of oxcarbazepine 60 mg/kg/day.

A monotherapy, rater-blind, trial in children (aged 1 month to 16 years) with inadequately controlled or new-onset partial seizures was conducted comparing two doses of oxcarbazepine. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria which was not statistically significant. The majority of patients in both treatment groups did not experience any video EEG-confirmed seizures during the study and completed this 5-day study without exiting.

It has been shown that oxcarbazepine has similar efficacy to other first line antiepileptic drugs (i.e. valproic acid, phenytoin and carbamazepine) with a statistically significantly better tolerability profile than phenytoin as judged by withdrawals due to adverse events and, a statistically significant longer retention rate (i.e. proportion of patients who stayed on treatment). Similar proportions of patients with partial and generalized tonic-clonic seizures, who were treated with oxcarbazepine, were seizure free over the 12 month treatment period of these trials.

NON-CLINICAL SAFETY DATA

Preclinical data indicated no special hazard for humans based on repeated dose toxicity, safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, monohydroxy derivative (MHD).

Immunotoxicity

Immunostimulatory tests in mice showed that MHD (and to a lesser extent oxcarbazepine) can induce delayed hypersensitivity.

Mutagenicity

Oxcarbazepine increased mutation frequencies in one Ames test *in vitro* in the absence of metabolic activation in one of five bacterial strains. Oxcarbazepine and MHD produced increases in chromosomal aberrations and/or polyploidy in the Chinese hamster ovary assay *in vitro* in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells *in vitro*. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an *in vivo* rat bone marrow assay.

Carcinogenicity

In the carcinogenicity studies, liver (rats and mice), testicular and female genital tract granular cell (rats) tumors were induced in treated animals. The occurrence of liver tumors was most likely a consequence of the induction of hepatic microsomal enzymes; an inductive effect which, although it cannot be excluded, is weak or absent in patients treated with oxcarbazepine (Trileptal®). Testicular tumors may have been induced by elevated luteinizing hormone concentrations. Due to the absence of such an increase in humans, these tumors are considered to be of no clinical relevance. A dose-related increase in the incidence of granular cell tumors of the female genital tract (cervix and vagina) was noted in the rat carcinogenicity study with MHD. These effects occurred at exposure levels comparable with the anticipated clinical exposure. The mechanism for the development of these tumors has not been fully elucidated but could be related to increased estradiol levels specific to the rat. The clinical relevance of these tumors is unclear.

Reproductive toxicity

For reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

None known.

STORAGE

Store at temperatures not exceeding 30°C.

Use within 7 weeks after first opening the bottle.

Do not use after the date marked “EXP” on the pack.

Drugs should be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Before taking oxcarbazepine (Trileptal®) oral suspension, the bottle should be shaken well and the dose prepared immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral syringe supplied. The amount should be rounded to the nearest 0.5 mL when using the 10 mL syringe (supplied with the bottle containing 250 mL for older children and adults) and to the nearest 0.1 mL when using the 1 mL syringe (supplied with the bottle containing 100 mL for younger children). Oxcarbazepine (Trileptal®) oral suspension may be swallowed directly from the syringe or can be mixed in a small glass of water just prior to administration. After each use, the bottle should be closed and the outside of the syringe wiped with a dry, clean tissue.

AVAILABILITY

Type III Brown Glass Bottle with a Child-Resistant Closure with Tamper-Proof Ring 100 mL with 1 mL and 5 mL Oral Dosing Syringes and Bottle Adapter (Box of 1’s)

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Registration Number: DRP-7461
First Registration Date: 29 October 1996

Manufactured by:
Delpharm Huningue S.A.S.
26, Rue De La Chapelle
Huningue, France

Imported by:
5th Floor, Ayala North Exchange Tower 1, Ayala Avenue,
Corner Salcedo and Amorsolo Streets, Makati City, Metro Manila

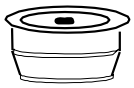
International Package Leaflet
Information issued: 19 June 2023

INSTRUCTIONS FOR USE

Please read these instructions carefully so that you know how to use the medicine dispensing system correctly.

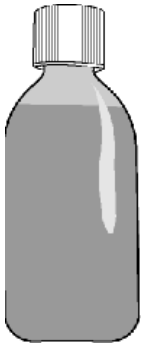
About the medicine dispensing system

There are 3 parts to the dispensing system:

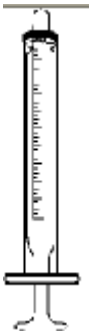


1. A **plastic adapter** that you push into the neck of the bottle the first time you open the bottle.

   The adapter must always remain in the bottle.

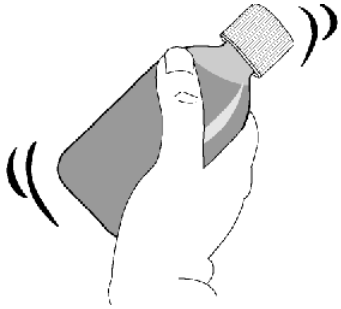


2. A **bottle** containing the medicine, with a child resistant cap. Always replace the cap after use.



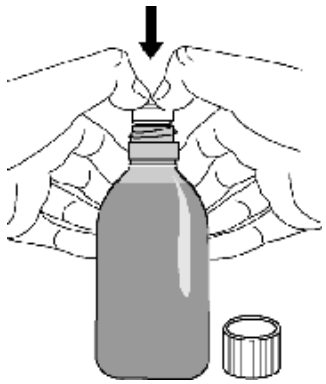
3. An **oral dosing syringe** that fits into the plastic adapter to withdraw the prescribed dose of medicine from the bottle.

Preparing the bottle



1. Shake the bottle of medicine for **at least 10 seconds.**
2. Remove the child resistant cap by pushing it f**irmly** down and turning it anti-clockwise (as shown on the top of the cap).

Note: Keep the cap safe to close the bottle after each use.



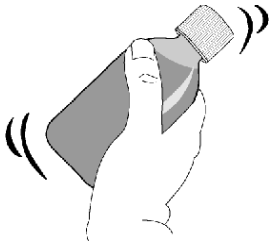
3. Hold the open bottle upright on a table and push the plastic adapter firmly into the neck of the bottle as far as you can.
4. Replace the cap to be sure that the adapter has been fully forced into the neck of the bottle.

Note: you may not be able to push the adapter fully down but it will be forced into the bottle when you screw the cap back on.

5. Now the bottle is ready to use with the syringe. The adapter must always stay in the bottle.

To dispense a dose, please follow all the instructions for **Taking the medicine**

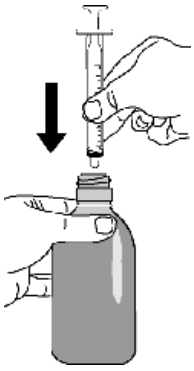
Taking the medicine



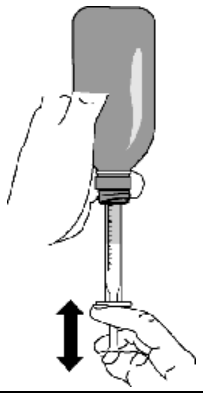
The medicine can be swallowed directly from the oral syringe, or mixed in a small glass of water.

1. Shake the bottle well. Prepare the dose right away.
2. Push and turn the child resistant cap to open the bottle.

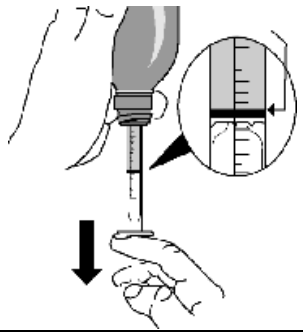
(Note: Always replace the cap after use)



3. Check the plunger is fully down inside the barrel of the oral syringe.
4. Keep the bottle upright and insert the oral syringe **firmly** into the plastic adapter.

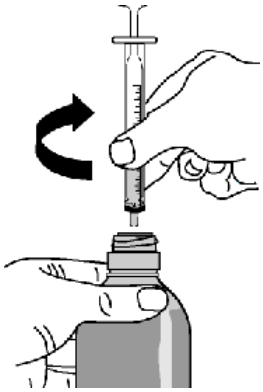


5. Hold the oral syringe in place and carefully turn the bottle upside down.
6. Slowly pull the plunger fully down so that the syringe fills with medicine. Push the plunger back up completely to expel any large air bubbles that may be trapped inside the oral syringe

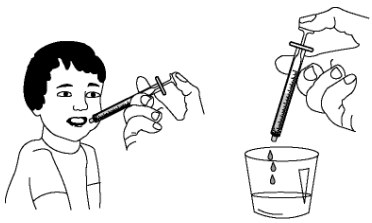


7. Withdrawing the prescribed dose: Slowly pull the plunger down until the top edge of the indicated ring is exactly level with the marker on the oral syringe barrel that indicates the prescribed dose.

Note: If the prescribed dose is more than can be measured in the syringe, you will need to reload the oral syringe to make up the full dose.



8. Carefully turn the bottle upright. Take out the oral syringe by gently twisting it out of the plastic adapter. The plastic adapter should stay in the bottle.



9. The dose of the medicine can be swallowed directly from the oral syringe (the patient must be sitting upright and the plunger must be pushed **slowly** to allow the patient to swallow). Alternatively, the dose can be mixed in a small glass of water just prior to administration. Stir and drink the entire mixture right away.
10. Replace the child resistant cap after use.
11. **Cleaning:** After use, wipe the outside of the syringe with a dry, clean tissue