

# CARBAMAZEPINE IN CHILDHOOD EPILEPSY

Report prepared for the World Health Organization  
October 2006

## **1. Summary statement of the proposal for inclusion, change or deletion**

Carbamazepine oral suspension (100mg/5ml), 100mg and 200mg chewable tablets are proposed for addition to the Model List of Essential Medicines, for use in the management of epilepsy in children. It is at least as effective as phenobarbitone, phenytoin and sodium valproate in the management of partial and tonic-clonic seizures in children.

## **2. Name of the focal point in WHO submitting or supporting the application**

Dr Tarun Dua, Management of Mental and Brain Disorders (MBD), Noncommunicable Diseases and Mental Health (NMH)  
Dr Martin Weber, Country Implementation Support (CIS), Family and Community Health (FCH).

## **3. Name of the organization(s) consulted and/or supporting the application**

None.

## **4. International Nonproprietary Name (INN, generic name) of the medicine**

Carbamazepine.

## **5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

Carbamazepine is available in the UK as a sugar free oral suspension of strength 100mg carbamazepine in 5ml (Tegretol<sup>®</sup>). Tegretol<sup>®</sup> is also available as 100mg, 200mg and 400mg tablets, 100mg and 200mg chewtabs and 200mg and 400mg modified release tablets.

There are also generic formulations of the solid dose preparations available. These may vary in bioavailability and it is suggested that to avoid reduced effect or excessive side-effects, care should be exercised if formulations need to be changed.

## **6. International availability - sources, if possible manufacturers**

Available in Australia, the United Kingdom and multiple other countries.

## **7. Whether listing is requested as an individual medicine or as an example of a therapeutic group**

As an individual medicine.

## **8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

Epilepsy is the most common serious neurological disorder and is one of the world's most prevalent noncommunicable diseases.

Due to differences in inclusion criteria, classification, diagnosis and case ascertainment methods, incidence and prevalence rates have varied considerably in different studies. If febrile seizures, neonatal seizures, single seizures or seizures in acute illnesses are included, the figures may be elevated several fold.

Data from the WHO<sup>(1)</sup> indicate there are over 50 million sufferers of epilepsy in the world today of whom 85% live in developing countries. Globally, there are an estimated 2.4 million new cases each year and at least 50% of these cases begin in childhood or adolescence.

Incidence is defined as the frequency of new cases of a disease in a defined population during a specified period of time (e.g. a calendar year).

When epilepsy is defined as recurrent, unprovoked seizures, the average annual incidence in developed countries is quoted between 40-70 per 100,000 of the general population<sup>(2,3,4,5,6)</sup>.

In developing countries, this figure is much higher at around 100-190 per 100,000 of the general population per year<sup>(4,5,6,7)</sup>. The main reason for the higher incidence of epilepsy in developing countries is the higher risk of experiencing a condition which can lead to permanent brain damage e.g. parasitic infection such as neurocysticercosis and malaria; meningitis; pre and perinatal complications and malnutrition.

The incidence of recurrent seizures is highest in the first year of life and declines thereafter throughout childhood and adolescence<sup>(4)</sup>. Incidence decreases from ~ 150 per 100,000 in the first year of life to ~ 60 per 100,000 at ages 5-9 years and 45-50 per 100,000 in older children<sup>(27)</sup>. Most studies that provide incidence rates separately for boys and girls find slightly higher total rates for boys<sup>(4)</sup>. This difference in sex-specific rates varies by age however as it is suggested that before 5 years, incidence rates are ~ 30-60% higher in girls than boys while rates tend to be 10-20% higher in boys through later childhood and adolescence<sup>(4)</sup>. Sex differences may reflect differences in predominant seizure types at different ages, differences in exposures to risk factors because of social differences in the rearing of male and female children and changes in susceptibility to seizures in boys and girls with age or variations in diagnosis by sex.

Prevalence is a measure of the number of new and existing cases (both new and old) of epilepsy in a defined population at either a specific point in time (point prevalence) or over a defined interval of time such as a year (period prevalence).

Again, like incidence rates, prevalence rates quoted can be influenced depending on whether persons with single seizures, febrile seizures, acute symptomatic seizures or only recurrent unprovoked seizures are counted as cases.

The usual prevalence figure quoted is ~ 5-10 cases per 1000 of the general population<sup>(3,4,5,6,7,27)</sup> (excluding febrile convulsions, single seizures and inactive cases). In children, estimates are of the order of 4-5 per 1000 children<sup>(2,4)</sup>

Prevalence rates increase with age ranging from ~ 2-3 per 1000 in children up to 7 years of age to 4-6 per 1000 at 11-15 years of age. Rates tend to be slightly higher in boys than in girls<sup>(4)</sup>.

Some studies report the prevalence of epilepsy in developing countries to be higher than that in developed countries with quoted prevalence figures of 10-15 per 1000 of the general population<sup>(4,5,6)</sup>. However, Scott RA et al<sup>(7)</sup> suggests that prevalence rates for active epilepsy are similar in both developing and industrialised countries. As the incidence of epilepsy is much higher in the former, it is suggested that a significant proportion of the affected population in developing countries may be dying from the seizure disorder or its underlying cause.

Geographic variation has been hard to assess because of a lack of standard techniques but a consistent finding is that prevalence rates are higher in rural than in urban areas<sup>(3)</sup>.

In developed countries, the prevalence of epilepsy is usually found to be slightly higher in the lower socio-economic groups<sup>(3)</sup>.

Since the aetiology of epilepsy is frequently multifactorial, the exact attribution of cause in the general population is often impossible. It has traditionally been said that 60-70% of all epilepsies have no clear cause and these are best referred to as cryptogenic epilepsies.

The annual incidence of epilepsy is relatively small and few studies have reported incidence cases by the type of seizure of epilepsy syndrome<sup>(4)</sup>. It has been suggested that 1/5th of recently diagnosed children and nearly ¾ of prevalent cases are reported to have experienced more than one type of seizure. These children are most often classified according to the predominant seizure type.

Generalised seizures are common in field studies, especially in developing countries, often because partial seizures are missed. In developed countries, over half the incidence cases are partial seizures. Partial and generalised seizures vary with age. Generalised seizures have the highest incidence in the first year of life. With the exception of absence seizures, for which incidence rates peak in 5-10 year olds, the incidence of generalised seizures in childhood declines after the first year of life. Incidence rates for partial seizures increase slightly during early childhood and remain relatively constant thereafter throughout childhood and adolescence. Among partial seizures, complex partial seizures are generally the most common<sup>(4,6)</sup>.

Given the correct treatment, epilepsy responds to treatment in up to 70% of patients. However, whilst 80% of the potential market for antiepileptic drugs is in the developing world, it is suggested that around ¾ of these people with epilepsy may not receive any or receive incorrect treatment. This is thought to be related to inadequacies in health care resources and delivery and also to the social stigma attached to the condition<sup>(1,5,7)</sup>.

Ideally, the choice of antiepileptic drug for each patient should be based on seizure type and/or the syndrome as well as the individual patient's needs.

In developing countries however, both the choice and the supply of drugs are limited. An analysis of the market suggests that while the use of older and cheaper drugs such as phenobarbitone has declined in developed, industrialised regions, the market share in developing countries is higher and increasing more quickly than that of the newer antiepileptic drugs. Alternative anti-epileptic drugs in developing countries are in very short supply and in such systems, the normal determinants for drug treatment are the drugs cost and availability and not necessarily efficacy and lack of adverse effects.

Phenobarbitone is the WHO's first line anti-epileptic drug in developing countries where it is the most commonly prescribed anti-epileptic drug. Indeed, in their review Scott RA et al<sup>(7)</sup> include a number of studies claiming phenobarbitone to be both effective and tolerated in patients with epilepsy treated in developing countries. However, whilst it is cheaper than other agents used frequently in developed countries (e.g. phenytoin, sodium valproate and carbamazepine), questions have been raised about its suitability with respect to its efficacy and profile of adverse effects. Certainly, in Europe and the USA, phenobarbitone is no longer considered a first line drug due to concerns over its efficacy and short and long-term tolerability.

Despite a lack of hard evidence from individual randomised controlled trials, there is a strong clinical recommendation in Europe and the USA, that carbamazepine is the first line treatment of choice for partial epilepsies<sup>(8,9,10,11,12,13,14)</sup>.

## **9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)**

For oral administration in children aged 1-12 years, an initial dose of 5mg/kg as a single dose at night or 2.5mg/kg/dose twice daily is recommended. This can be increased, as necessary by 2.5-5mg/kg every 3-7 days to a usual maintenance dose of 5mg/kg/dose 2-3 times daily. The maximum suggested dose is 20mg/kg/DAY<sup>(28)</sup>.

For oral administration in children and adolescents over 12 years of age, an initial dose of 100-200mg/dose 1-2 times daily is recommended. This can be increased slowly, as necessary to a usual maintenance dose of 400-600mg/dose 2-3 times daily. Maximum dose in patients over 12 years of age is 2000mg/DAY<sup>(28)</sup>.

## **10. Summary of comparative effectiveness in a variety of clinical settings**

The mechanism of action of carbamazepine has only been partially elucidated. Carbamazepine stabilizes hyperexcited nerve membranes, inhibits repetitive neuronal discharges and reduces synaptic propagation of excitatory impulses. It is possible that prevention of repetitive firing of sodium-dependent action potentials in depolarized neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

The few studies / reviews identified from an extensive literature search suggest relatively equal efficacy between phenobarbitone, carbamazepine, sodium valproate and phenytoin in the treatment of partial seizures and tonic-clonic seizures in children. Very similar (and effective) rates of response are generally achieved with these agents in

these patients and it may be that the main determinant for which drug is best for the patient is the side-effect profile for that particular patient.

In 2003, The Cochrane Collaboration<sup>(14)</sup> compared carbamazepine with phenobarbitone monotherapy for epilepsy. The purpose of this review was to assess the effects of carbamazepine compared with phenobarbitone for people with partial onset seizures (simple/complex partial or secondarily generalised seizures) or generalised onset tonic-clonic seizures (with or without other generalised seizure types). The studies included were randomised or quasi-randomised, blinded or non-blinded controlled trials in children or adults. The outcome measures considered were

- time to withdrawal of allocated treatment (due to lack of efficacy or intolerable adverse effects)
- time to 12 month remission
- time to first seizure

Data from 684 participants (from 4 trials representing 59% of the participants recruited into the 9 trials that met inclusion criteria) was included. Results indicate that time to treatment withdrawal is significantly improved with carbamazepine compared to phenobarbitone. Results for time to first seizure and time to 12 month remission show no overall advantage for either drug.

Subgroup analyses for time to 12 month remission find no evidence of an interaction between seizure type and treatment but do show a trend in favour of carbamazepine for generalised onset seizures and no difference for partial onset seizures.

Results for time to first seizure also show no overall advantage for either drug. Subgroup analyses show a significant interaction between treatment and seizure type with phenobarbitone favoured for partial onset seizures and a trend in favour of carbamazepine for generalised onset seizures.

Hence, for both seizure outcomes there is a trend in favour of carbamazepine for generalised-onset seizures. This is unexpected given anecdotal evidence that carbamazepine may worsen generalised onset seizure types such as absence or myoclonus.

For time to first seizure, the significant advantage for phenobarbitone treating partial onset seizures is also unexpected given that current guidelines recommend carbamazepine as the drug of choice in the treatment of partial seizures.

However, despite these findings, the results do not provide robust evidence upon which to base a choice between these two drugs in terms of seizure control.

The reviewers made the following conclusions:

- overall there is a clear advantage for carbamazepine for time to treatment withdrawal indicating that this drug is significantly better tolerated than phenobarbitone
- for seizure outcomes, there were trends in favour of phenobarbitone for partial onset seizures and carbamazepine for generalised-onset seizures. These do not however provide reliable evidence upon which to base a choice
- overall results indicate that of the two drugs investigated, carbamazepine would be the better choice for people with either partial or generalised onset seizure types.

However, given reports of carbamazepine worsening certain seizure types, it is not considered a drug of first choice for individuals with a generalised seizure disorder

The randomised, comparative trial conducted by de Silva et al 1996<sup>(15)</sup>, was included in the above Cochrane Review and was the only study recruiting children only. In this long-term, prospective, randomised trial, the efficacy and tolerability of phenobarbitone, phenytoin, carbamazepine and sodium valproate were compared in 167 children aged 3-16 years with at least 2 previously untreated tonic-clonic or partial seizures. Children under the age of 3 years and those with myoclonic, absence, tonic or drop attacks were excluded.

Patients were randomly assigned to one of the four anti-epileptic drugs (identity of treatment was not masked) and were started on a small dose calculated on body weight with dosage increments as required and as tolerated until seizures ceased or until the blood concentration was in the top half of the recommended optimum range. Seizure type and frequency were recorded. If seizures continued, monotherapy was deemed to have failed and either another drug was chosen by the physician or a second drug, usually carbamazepine was added.

Efficacy was assessed by time to first seizure after the start of treatment and time to achieving 1 year remission.

Results showed no significant differences in efficacy between phenobarbitone, phenytoin, carbamazepine and sodium valproate.

The outcome with each of the drugs was good with 12-25% (overall 20%) of children remaining seizure free at 3 years follow-up and 60-80% (overall 73%) achieving a 1 year remission by 3 years of follow-up. Comparison of the 4 drugs included an adjustment for seizure type and analysis showed no significant influence of the two different seizure categories on the comparative efficacy.

However, randomisation to phenobarbitone was discontinued early in the study period due to unacceptable side-effects. Six of the first 10 children allocated phenobarbitone had adverse effects (behavioural or cognitive) that necessitated withdrawal of the drug. Because of this unacceptably high rate of adverse effects, no further children were assigned phenobarbitone.

Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatment compared with 9% of children on phenytoin.

Again, despite a lack of hard evidence from individual randomised controlled trials, there is a strong clinical belief that sodium valproate is the drug of choice for generalised epilepsies and carbamazepine for partial epilepsies. A Cochrane Review in 2000<sup>(13)</sup> compared carbamazepine with sodium valproate monotherapy in the treatment of epilepsy.

The studies included in the review were randomised controlled monotherapy studies comparing carbamazepine and sodium valproate and included children or adults with partial onset seizures (simple partial, complex partial or secondarily generalising tonic-clonic seizures) or generalised onset tonic-clonic seizures.

1256 participants from 5 trials (representing 85% of the participants recruited into the 8 trials available) met the inclusion criteria. The intervention was carbamazepine or sodium valproate monotherapy. The primary outcome measure was time to withdrawal of allocated treatment (i.e. treatment was withdrawn for poor seizure control or adverse effects or both, or additional add-on treatment was initiated). Secondary outcomes were time to 12-month remission from seizures and time to first seizure post-randomisation.

Results from this review did not find an overall difference between carbamazepine and sodium valproate for the primary global outcome time to treatment withdrawal. For efficacy outcomes, the analysis for time to first seizure found a significant interaction between treatment and epilepsy type, where patients with a partial epilepsy do better on carbamazepine. For time to 12 month remission, results for the subgroup of people with a partial epilepsy indicate a significant advantage for carbamazepine, although the test for an interaction between treatment and epilepsy type was not significant. These results do not provide outright evidence in favour of carbamazepine for people with a partial epilepsy, however they are in keeping with prior clinical belief and support the policy of using carbamazepine as the treatment of choice for patients with a partial epilepsy.

Verity CM et al, on behalf of the Paediatric EPITEG Collaborative Group, reported on a multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy<sup>(16)</sup>. 260 children with primary generalised epilepsy or with partial epilepsy (with or without secondary generalisation) at 63 outpatient clinics in the UK and Ireland participated in a 3-year study. Children aged 5-16 years were included and randomised to receive either sodium valproate or carbamazepine. For both drugs, treatment was initiated at a fairly low dose and increased as necessary until seizures were controlled or until toxic symptoms appeared. Maximum daily dose for sodium valproate was 30mg/kg/DAY and for carbamazepine 20mg/kg/DAY. No other antiepileptic medication was allowed – the necessity for additional anticonvulsant medication during the treatment period was classed as treatment failure.

The analysis of treatment failures (i.e. drug withdrawal following unacceptable adverse events, inadequate seizure control or both), showed that there was little difference in failure rates between the drugs. Remission analysis showed that there was no difference in the overall efficacy between sodium valproate and carbamazepine in controlling either generalised or partial seizures. Both drugs achieved a high degree of seizure control with 75% of patients having at least 12 months and 45-55% at least 2 years, of freedom from seizures.

Treatment was withdrawn because of adverse effects in 12% patients on carbamazepine and 15% patients on sodium valproate. Only 5 (3%) children on carbamazepine were withdrawn because of rashes in the first few months of treatment which is far lower than that reported in the EPITEG Study in adults when 9% of patients on carbamazepine had severe rashes.

As stated earlier, carbamazepine is considered as first-line treatment in many countries both for partial seizures and generalised tonic-clonic seizures. However, in the USA phenytoin is more commonly used and in preference to carbamazepine. Studies of the two drugs have not shown differences in efficacy between them and it is suggested that the difference in the European and US approach relates to perceived differences in adverse effect profiles.

In 2002, The Cochrane Collaboration produced a review of carbamazepine versus phenytoin monotherapy for epilepsy<sup>(17)</sup>. The purpose of this was to review the best evidence comparing carbamazepine and phenytoin when used as monotherapy in people with partial onset seizures or generalised onset tonic-clonic seizures with or without other generalised seizure types. Randomised controlled trials of adults and children were included as long as they included a comparison of carbamazepine monotherapy with phenytoin monotherapy.

Outcomes used were

- time to withdrawal of allocated treatment
- time to 12 month remission
- time to 6 month remission
- time to first seizure post randomisation

Data for 551 participants from three trials was available (representing 61% of the participants recruited into the nine trials that fulfilled the inclusion criteria). Results suggested no overall difference between carbamazepine and phenytoin for any of these outcomes.

There are some newer antiepileptic agents now available in Europe and the USA which have been developed both for their efficacy and also with claims of an improved side-effect profile over older agents such as carbamazepine.

A Cochrane Review in 2006<sup>(18)</sup> reviewed the best evidence comparing carbamazepine with one of the newer agents lamotrigine when used as monotherapy in people with partial onset or generalised onset tonic-clonic seizures with or without other generalised seizure types. This review includes randomised controlled trials in adults and children who were randomised to receive either carbamazepine or lamotrigine. The outcomes monitored were

- time to treatment withdrawal (due to lack of efficacy or adverse effects)
- time to first seizure post-randomisation
- seizure freedom at 6 months

Data for 1384 participants from 5 trials were included and results showed that time to treatment withdrawal was significantly improved with lamotrigine compared to carbamazepine. Time to first seizure and seizure freedom at 6 months favoured carbamazepine and although the results were not statistically significant, suggest a potentially important advantage for carbamazepine.

The reviewers conclude that lamotrigine is significantly less likely to be withdrawn than carbamazepine (i.e. is better tolerated); results for time to first seizure suggest that carbamazepine may be superior in terms of seizure control.

Carbamazepine has also been compared with other newer and more expensive anti-epileptic drugs, such as vigabatrin and topiramate. In general, it is suggested that the efficacy of carbamazepine compared with vigabatrin or topiramate is similar although the newer agents may be better tolerated.

In 1999, Chadwick D et al<sup>(19)</sup> reported on a multicentre randomised double-blind study of 459 patients with newly diagnosed, untreated partial epilepsy who were randomly

assigned to receive carbamazepine 600mg daily or vigabatrin 2g daily. The time to withdrawal for lack of efficacy or adverse effects did not differ between the groups. Vigabatrin was better tolerated than carbamazepine but was more frequently associated with psychiatric symptoms and weight gain. All efficacy outcomes favoured carbamazepine.

Zamponi N et al<sup>(20)</sup> conducted an open comparative long-term study of vigabatrin versus carbamazepine in newly diagnosed partial seizures in children. 70 children were given either vigabatrin (50-60mg/kg/DAY) or carbamazepine (15-20mg/kg/DAY) and results showed efficacy of the two drugs to be similar with the suggestion of a better side-effect profile with vigabatrin.

Wheless JW et al<sup>(21)</sup> reported on a double blind comparison of topiramate, carbamazepine and sodium valproate in 613 patients of whom 119 were children or adolescents. Topiramate was compared with the investigators choice of carbamazepine or sodium valproate as first-line therapy. No differences were seen between the drugs in efficacy measures. Topiramate at the target dose of 100mg/DAY in children and adolescents was associated with the fewest discontinuations owing to adverse effects.

## **11. Summary of comparative evidence on safety**

### **Adverse effects<sup>(22)</sup>**

All antiepileptic drugs have a relatively high incidence of adverse reactions. They are a major cause of discontinuing treatment. Many adverse reactions are dose related and predictable and can be minimised by commencing therapy with a low dose and with gradual escalation of the dose and dose reduction if symptoms persist.

With respect to carbamazepine, particularly at the start of treatment or if the initial dose is too high, the following certain types of adverse reaction can occur very commonly (>10%) or commonly (>1% to <10%)

- CNS (dizziness, ataxia, drowsiness, fatigue, headache, diplopia, accommodation disorders)
- SKIN (allergic skin reactions, urticaria)
- GI DISTURBANCES (nausea and vomiting, dry mouth)
- BLOOD DYSCRASIAS (leucopenia, thrombocytopenia)
- LIVER DISTURBANCES (elevated gamma-glutamyl transferase and alkaline phosphatase). It is generally recommended that white blood cell counts and liver functions tests are conducted before commencing treatment and periodically thereafter
- ENDOCRINE SYSTEM AND METABOLISM (oedema, fluid retention, weight increase, hyponatraemia)

Occurrence of CNS adverse effects may be a manifestation of relative overdosage or significant fluctuation in plasma levels. Monitoring of plasma levels may be useful as is division of the daily dosage into 3-4 doses.

Idiosyncratic reactions can also occur<sup>(8,10,11,22)</sup>. These usually arise early in treatment but can occur at any time and are potentially serious (e.g. Stevens Johnson Syndrome, exfoliative dermatitis, hepatitis).

In their randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine and sodium valproate, de Silva et al<sup>(15)</sup> found a frequency of unacceptable adverse effects of 4% for carbamazepine and sodium valproate compared to 9% patients on phenytoin and 60% (6/10) patients given phenobarbitone. Of the two patients on carbamazepine who discontinued treatment, one was due to drowsiness and the other due to a blood dyscrasia. The authors also suggested that hypersensitivity reactions to carbamazepine seem to be less common in children than in adults.

The Cochrane Review in 2003<sup>(14)</sup> concluded that phenobarbitone was significantly more likely to be withdrawn than carbamazepine indicating it is less well tolerated than the latter.

In the Cochrane Review of 2000<sup>(13)</sup> comparing monotherapy of carbamazepine with sodium valproate, no significant difference in tolerance was noted between the two agents.

The incidence of adverse effects and the adverse effect profile of carbamazepine have also been compared with some of the newer agents. The Cochrane Review 2006<sup>(18)</sup> suggests that, although of comparable efficacy, lamotrigine is better tolerated than CBZ.

One of the studies included in the above review was a study published by Brodie MJ et al in 1995<sup>(23)</sup>. This was a double-blind comparison of lamotrigine and carbamazepine in patients aged 13 years and over with newly diagnosed epilepsy. Patients were randomised to increasing doses of lamotrigine or carbamazepine for 6 weeks until patients were receiving either 150mg lamotrigine daily or 600mg carbamazepine daily. For the next 24 weeks, doses were adjusted according to efficacy, tolerance and drug serum levels. Results for 151 patients showed both agents to be equally effective with 39% lamotrigine patients and 38% carbamazepine patients seizure free for the last 6 months of the study. The authors did report that lamotrigine was better tolerated with more patients able to complete the study period than patients treated with carbamazepine. Sleepiness was significantly more common with carbamazepine than with lamotrigine.

However, there were a number of subsequent comments to this study suggesting that the initial dose (300mg daily) and the escalation rate of carbamazepine were too great and that these could be responsible for the higher incidence of adverse effects. To minimise adverse effects, carbamazepine should be initiated at low dose with a slow dosage incremental rate.

Topiramate<sup>(21,24)</sup> and vigabatrin<sup>(25,26)</sup> have also been shown to have a similar efficacy to carbamazepine but these studies also suggest an improved adverse effect profile compared to carbamazepine.

Carbamazepine should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate seizures<sup>(22)</sup>.

## **Drug interactions<sup>(22)</sup>**

Cytochrome P450 3A4 is the main enzyme catalysing formation of carbamazepine 10,11-epoxide.

Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations which could induce adverse reactions.

Agents that may raise carbamazepine plasma levels include – isoniazid, ritonavir, macrolide antibiotics, azoles, terfenadine and protease inhibitors for HIV treatment.

Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

Agents that may decrease carbamazepine plasma levels include – phenobarbitone, primidone, theophylline, rifampicin and possibly clonazepam, valproic acid and oxcarbazepine (however, valproic acid and primidone have been reported to raise the plasma level of the pharmacologically active carbamazepine 10,11-epoxide metabolite). Mefloquine may antagonise the anti-epileptic effect of carbamazepine.

Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement: levothyroxine, clobazam, clonazepam, ethosuximide, primidone, valproic acid, corticosteroids, cyclosporine, digoxin, indinavir, saquinavir, ritonavir.

## **Use in Pregnancy<sup>(22)</sup>**

Pregnant women with epilepsy should be treated with special care. In women of childbearing age, carbamazepine should, wherever possible, be given as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of anti-epileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy.

If pregnancy occurs in a woman on carbamazepine therapy or if therapy with carbamazepine needs to be initiated during pregnancy, the drug's potential benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy. Minimum effective doses should be given and monitoring of plasma levels is recommended.

Babies born to epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major anti-epileptic drugs, increases the risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking<sup>(22)</sup>. However, there are reports of developmental disorders and malformations, including spina bifida and other congenital abnormalities in association with carbamazepine therapy.

Folic acid supplementation is recommended before and during pregnancy.

## **Use in Lactation<sup>(22)</sup>**

Carbamazepine passes into the breast milk (25-60% of the plasma concentration). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking carbamazepine may breast-feed their infants provided the infant is observed for adverse reactions.

### **13. Licensed Status**

Carbamazepine has a product licence in Europe and the USA for the treatment of partial seizures and tonic-clonic seizures in adults and children.

### **14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)**

British Pharmacopoeia.

### **15. Proposed (new/adapted) text for the WHO Model Formulary**

To be provided.

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