IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0540/149/003
Case No: 2081454

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Epi-Chrono 500 mg Prolonged-Release Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **13/07/2010** until **23/08/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epi-Chrono 500 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Epichrono 500 mg prolonged-release tablet contains 333 mg sodium valproate and 145 mg valproic acid, equivalent to 500 mg sodium valproate.

This product contains 46.08 mg of sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
Violet, oblong, biconvex, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of generalised, partial or other epilepsy.

In certain cases EpiChrono may be an appropriate choice for women of childbearing potential, provided that an informed choice has been made, based on a very careful evaluation, by the patient together with her treating physician, of all relevant elements (see 4.6 Pregnancy and Lactation).

4.2 Posology and method of administration

EpiChrono Prolonged Release Tablets are for oral administration.

EpiChrono is a prolonged release formulation which reduces peak concentration and ensures more even plasma concentrations throughout the day.

EpiChrono may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight.

In patients where adequate control has been achieved EpiChrono formulations are interchangeable with other Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:
Adults
Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20-30 mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg
Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg

An alternative formulation of Epilim should be used in this group of patients, due to the tablet size and need for dose titration. Epilim Liquid (sugar-free) or Epilim Syrup are alternatives.

Elderly
Although the pharmacokinetics of EpiChrono are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

Combined Therapy
When starting EpiChrono in patients already on other anticonvulsants, these should be tapered slowly; initiation of EpiChrono therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of EpiChrono. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

-Active liver disease
-Personal or family history of severe hepatic dysfunction, especially drug related
-Hypersensitivity to sodium valproate
-Porphyria

4.4 Special warnings and precautions for use

Stopping treatment may lead to an immediate relapse of the underlying symptoms; care should therefore be taken when consideration is being given to the withdrawal of treatment.

The concomitant use of valproic acid/sodium valproate and carbapenem agents is not recommended (see section 4.5)

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been exceptionally reported.
Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.
In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.
These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.
Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of EpiChrono therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Pancreatitis: Severe pancreatitis, which may result in fatalities, has been very rarely reported. Patients experiencing acute abdominal pain should have a prompt medical evaluation. Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, EpiChrono should be discontinued.

Women of childbearing potential
A decision to use EpiChrono in women of childbearing potential should only be taken after very careful evaluation, if the benefits of its use outweigh the risks of congenital anomalies to the unborn child. This decision is to be taken; before EpiChrono is prescribed for the first time as well as before a woman already treated with sodium valproate is planning a pregnancy.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

4.4.2.Precautions

Liver function tests should be carried out before therapy (see section 4.3 Contraindications), and periodically during the first 6 months, especially in patients at risk (see section 4.4.1 Special warnings).
As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they

are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Children: Monotherapy is recommended in children under the age of 3 years when prescribing EpiChrono, but the potential benefit of EpiChrono should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see section 4.4.1 Special warnings).

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity.

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of EpiChrono, the potential benefit of EpiChrono should be weighed against its risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with EpiChrono.

Diabetic patients: EpiChrono is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see 4.8 Undesirable Effects).

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1. Effects of EpiChrono on Other Drugs

- Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
EpiChrono may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate therapy may significantly increase the risk of certain adverse events associated with olanzapine.

- Phenobarbital
EpiChrono increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
EpiChrono increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin
EpiChrono decreases phenytoin total plasma concentration. Moreover EpiChrono increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine

Clinical toxicity has been reported when EpiChrono was administered with carbamazepine as EpiChrono may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

The risk of rash may be increased by co-administration of lamotrigine with valproic acid when lamotrigine is added on to valproic acid. EpiChrono may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***

EpiChrono may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

4.5.2. Effects of Other Drugs on EpiChrono

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and EpiChrono may increase valproic acid plasma concentration. EpiChrono dosage should be monitored.

Mefloquine and chloroquine increase valproic acid metabolism and have a convulsing effect. They may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. The dosage of EpiChrono may need adjustment accordingly.

In case of concomitant use of EpiChrono and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.
Decreases in blood levels of valproic acid have been reported when it is co-administered with ***carbapenem agents*** resulting in a 60-100% decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid is not considered to be manageable and therefore should be avoided (see section 4.4)

Colestyramine may decrease the absorption of EpiChrono.
Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3. Other Interactions

Caution is advised when using EpiChrono in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and ***topiramate*** has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

EpiChrono usually has no enzyme-inducing effect; as a consequence, EpiChrono does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Pregnancy and lactation

In certain cases EpiChrono may be an appropriate choice for women of childbearing potential, provided that an informed choice has been made, based on a very careful evaluation, by the patient together with her treating physician, of all relevant elements.

4.6.1. Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of EpiChrono during pregnancy has

been described as follows:

- Risk associated with seizures
During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.

- Risk associated with EpiChrono
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.
There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate when compared to the incidence for certain other antiepileptic drugs. EpiChrono use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.
Data suggest that antiepileptic polytherapy including EpiChrono induces a higher teratogenic risk than monotherapy with valproate only. Data have suggested an association between in-utero EpiChrono exposure and a risk of developmental delay particularly of verbal IQ in children born to mothers suffering from epilepsy and treated with valproate. Developmental delay is frequently associated with malformations and/or dysmorphic features. However, it is difficult to establish causal relationship in view of possible confounding factors such as low maternal or paternal IQ, genetic, social and environmental factors, and poor maternal seizure control during pregnancy.
Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
Women of childbearing potential should be informed of the risks and benefits of the use of EpiChrono during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before EpiChrono is prescribed for the first time or a woman already treated with EpiChrono is planning a pregnancy.

If a woman plans pregnancy, this provides an opportunity to review the need for anti-epileptic treatment whatever the indication. In bipolar disorders indication, cessation of EpiChrono prophylaxis should be considered. If, in any indication, further to a careful evaluation of the risks and benefits, EpiChrono treatment is continued during the pregnancy, it is recommended to use EpiChrono in divided doses over the day at the lowest effective dose. The use of prolonged release formulation may be preferable to any other treatment form.

In addition, if appropriate, folate supplementation should be started before pregnancy and at relevant dosage (5 mg daily) as it may minimize the risk of neural tube defects.

During pregnancy, EpiChrono anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk.

Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformations. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).

- Risk in the neonate
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2. Lactation

Excretion of EpiChrono in breast milk is low, with a concentration between 1% to 10% of total maternal serum levels. Based on literature and clinical experience, breastfeeding can be envisaged, taking into account the EpiChrono safety profile, especially haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Use of EpiChrono may provide seizure control such that the patient may be eligible to hold a driving licence. Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

Congenital, familial and genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepatobiliary disorders: rare cases of liver injury (see section 4.4.1. Special warnings)

Gastrointestinal disorders: (nausea, abdominal pain upper, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking EpiChrono with or after food or by using Enteric Coated Epilim.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion, occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Ataxia and transient and/or dose related fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Cases of isolated and moderate hyperammonaemia without change in liver function may occur frequently and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur EpiChrono should be discontinued.
Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Metabolic and nutrition disorders:
Very rare cases of hyponatremia have been reported.
Syndrome of Inappropriate Secretion of ADH (SIADH)

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopoenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.
Bone marrow failure, including pure red cell aplasia. Agranulocytosis.Isolated findings of a reduction in blood fibrinogen and/or increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (EpiChrono has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders:
Very rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme, rash.

Transient and/or dose related alopecia, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously.

Reproductive system and breast disorders:
Amenorrhoea and dysmenorrhea have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear and labyrinth disorders:
Deafness, either reversible or irreversible has been reported rarely.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) but the mode of action is as yet unclear.
Very rare cases of enuresis have been reported.

Immune system disorders:
Angioedema, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.
Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

Psychiatric disorders:
Confusion

General disorders and administration site conditions:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Since it is a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Special Precautions for Use).

4.9 Overdose

Cases of accidental and deliberate EpiChrono overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic: gastric lavage, cardio-respiratory monitoring.
Haemodialysis and haemoperfusion have been used successfully.
Naloxone has also been used in a few isolated cases. In cases of massive overdose, hemodialysis and hemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Valproic acid and sodium valproate are anticonvulsants.
The most likely mode of action for EpiChrono is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.
In certain in vitro studies, it has been reported that EpiChrono can stimulate HIV. However this effect is modest, variable, unrelated to the dose and not documented in man.

5.2 Pharmacokinetic properties

The half-life of EpiChrono is usually reported to be within the range of 8-20 hours. It is usually shorter in children. The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of EpiChrono may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

EpiChrono formulations are prolonged release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and prolonged release Epilim formulations.
In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of EpiChrono make the measurement of plasma levels less dependent upon time of sampling.
The EpiChrono formulations are bioequivalent to Epilim Liquid and Enteric Coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of EpiChrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Ethylcellulose
Hydrated silica

Film coat
Titanium dioxide (E171)
Erythrosine (E127)
Indigo carmine (E132)
Black iron oxide (E172)
Hypromellose (E464)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

PVC/aluminium laminate blister packs in cardboard cartons. Pack size: 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 540/149/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 24th August 2007

10 DATE OF REVISION OF THE TEXT

July 2010