# PROFESSIONAL INFORMATION FOR

# EPITEC 25 / 50 / 100 / 200 TABLETS

## SCHEDULING STATUS

**S3**

## 1 NAME OF THE MEDICINE

**EPITEC 25** Tablets

**EPITEC 50** Tablets

**EPITEC 100** Tablets

**EPITEC 200** Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

| | |
|---|---|
| EPITEC 25 | Each tablet contains lamotrigine 25 mg.<br>Contains sugar: lactose monohydrate 52,50 mg per tablet. |
| EPITEC 50 | Each tablet contains lamotrigine 50 mg.<br>Contains sugar: lactose monohydrate 105,50 mg per tablet. |
| EPITEC 100 | Each tablet contains lamotrigine 100 mg.<br>Contains sugar: lactose monohydrate 211,00 mg per tablet. |
| EPITEC 200 | Each tablet contains lamotrigine 200 mg. |

Contains sugar: lactose monohydrate 420,00 mg per tablet.

For full list of excipients, see **section 6.1.**

## 3 PHARMACEUTICAL FORM

Tablets

EPITEC 25: Yellow, round, circular tablets with 25 debossed on one side and breakline on the other side.

EPITEC 50: White, round, circular tablets with 50 debossed on one side and breakline on the other side.

EPITEC 100: White, round, circular tablets with 100 debossed on one side and breakline on the other side.

EPITEC 200: Yellow, capsule-shaped, biconvex tablets with 200 debossed on one side and plain on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**EPILEPSY**

***Adults and children over 12 years***

EPITEC is indicated:

- As monotherapy or as an add-on treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures;
- and in the treatment of primary generalised tonic-clonic seizures.

***Children 2 – 12 years***

EPITEC is indicated as add-on treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures not satisfactorily controlled with other antiepileptic medicines.

Monotherapy in children under 12 years of age is not recommended.

***Lennox-Gastaut syndrome***

EPITEC is indicated as add-on treatment of seizures associated with this syndrome.

**BIPOLAR DISORDER**

***Adults 18 years of age and over***

EPITEC is indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

## 4.2 Posology and method of administration

It is important to adhere to the recommended dosages, especially in combination therapy with valproate where one-tenth to one-fifth of the normal dose is administered.

Do not exceed the maximum dosage (see **section 4.4**).

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to bodyweight, do not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

***Restarting therapy***

Considering the risk of serious rash associated with high initial doses and exceeding the recommended dose escalation for EPITEC, prescribers should evaluate the need for increasing the dose to maintenance when restarting EPITEC in patients who have discontinued EPITEC for any reason (see **section 4.4**). The greater the interval of time since the previous dose, the more consideration should be given to escalation to maintenance dose. When the interval since discontinuing EPITEC exceeds five half-lives (see **section 5.2**), EPITEC should generally be escalated to the maintenance dose according to the appropriate schedule. If EPITEC was discontinued in patients due to rash associated with previous treatment, it is recommended that treatment not be restarted.

**EPILEPSY**

When concomitant antiepileptic medicines are withdrawn to achieve EPITEC monotherapy or other antiepileptic medicines are added-on to treatment regimens containing EPITEC, consideration should be given to the effect this may have on EPITEC pharmacokinetics (see **section 4.5**). To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed as weight changes occur. If the calculated dose (e.g. for use in children and patients with hepatic impairment), according to body weight, does not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

**Posology**

**Monotherapy: Adults and children over 12 years**

Initially 25 mg once daily for 2 weeks, followed by 50 mg once daily for 2 weeks. Thereafter dosage should be increased by maximum 50 – 100 mg every 1 – 2 weeks until optimal response is achieved.

**Usual maintenance dose:** 100 – 200 mg/day administered once a day or as 2 divided doses. Sometimes doses of up to 500 mg/day of EPITEC were required to achieve the desired response.

To minimise the risk of skin rash, the recommended initial dose and subsequent dose escalation should not be exceeded (see **section 4.4**).

**Add-on therapy: Adults and children over 12 years not taking sodium valproate**

Patients taking co-administrated antiepileptic medicines or other medicines (see **section 4.5**) that induce lamotrigine glucuronidation with/without other antiepileptic medicines (except valproate):

Initially 50 mg once daily for 2 weeks, followed by 100 mg/day in 2 divided doses for 2 weeks. Thereafter, dosage should be increased by maximum 100 mg every 1 – 2 weeks until optimal response is achieved.

**Maintenance dose:** Between 200 – 400 mg/day administered in 2 divided doses.

**Patients taking sodium valproate, with or without any other antiepileptic medicines**

Initially 25 mg every alternate day for 2 weeks followed by 25 mg once a day for 2 weeks. Thereafter the daily dose is increased by a maximum of 25 – 50 mg every 1 – 2 weeks until optimal response is achieved.

**Maintenance dose:** Between 100 – 200 mg/day given once a day or in 2 divided doses. Do not exceed recommended initial dose.

**Patients taking oxcarbazepine**

Patients taking oxcarbazepine 1 200 mg daily, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial EPITEC dose is 25 mg once daily for 2 weeks, followed by 50 mg once daily for two weeks. Thereafter the dose should be increased by a maximum of 50 - 100 mg every 1 - 2 weeks until optimal response is achieved or a dose of 200 mg is reached.

**Maintenance dose**: (to achieve optimal response): 100 - 200 mg/day once a day or as two divided doses.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see **section 4.4**).

**Children 2 – 12 years: Patients not taking sodium valproate**

The weight of a child must be monitored and the dose reviewed as weight changes occur to ensure that a therapeutic dose is maintained. The dose to be administered to children is that equal to the lower number of whole tablets, if the dose calculated according to body weight does not equate to whole tablets.

In those patients taking concomitant antiepileptic medicines (AEMs) or other medicines (see **section 4.5**) that induce lamotrigine glucuronidation with/without other antiepileptic medicines (except valproate), the dose is as follows:

Initially 0,6 mg/kg body mass per day in 2 divided doses for 2 weeks, followed by 1,2 mg/kg body mass per day for 2 weeks. Thereafter the dose should be increased by a maximum 1,2 mg/kg every 1 – 2 weeks until optimal response is achieved.
**Usual maintenance dose:** 5 – 15 mg/kg/day in 2 divided doses. Maximum daily dose of 400 mg should not be exceeded.

**Patients taking sodium valproate (with or without any other antiepileptic medicines):**

Initially 0,15 mg/kg body mass per day once daily for 2 weeks, followed by 0,3 mg/kg/day once a day for 2 weeks. Thereafter increase dose by maximum 0,3 mg/kg every 1 – 2 weeks until optimal response is achieved.
**Usual maintenance dose**: 1 – 5 mg/kg/day once daily or in 2 divided doses. Maximum daily dose of 200 mg should not be exceeded. Patients aged 2 – 6 years may require a maintenance dose at the higher end of the scale.

**Patients taking oxcarbazepine**

In patients taking oxcarbazepine, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial EPITEC dose is 0,3 mg/kg bodyweight/day given once a day or in two divided doses for 2 weeks, followed by 0,6 mg/kg/day given once a day or in

two divided doses for 2 weeks. Thereafter the dose should be increased by a maximum of 0,6 mg/kg every 1 – 2 weeks until optimal response is achieved or a dose of 200 mg is reached.

**Usual maintenance dose:** (to achieve optimal response): 1 – 10 mg/day given once a day or as two divided doses, with a maximum of 200 mg/day.

**NOTE:** In patients taking other antiepileptic medicines, where data on the pharmacokinetic interaction between EPITEC and that medicine are currently not available, dose increases of EPITEC should follow the recommendations as for patients on concurrent sodium valproate. Thereafter, the dose should be escalated until the optimal response is achieved.

To minimise the risk of skin rash, the recommended initial dose and subsequent dose escalation should not be exceeded (see **section 4.4**).

**Dosage in seizures associated with Lennox-Gastaut syndrome**

EPITEC doses for the treatment of seizures associated with Lennox-Gastaut syndrome correspond to the dosing guidelines outlined above for both adults and children aged 2 to 12 years.

**BIPOLAR MOOD DISORDER**

Due to the risk of rash, the initial dose and subsequent dose escalation of EPITEC should not be exceeded (see **section 4.4**)

EPITEC is recommended for use in bipolar patients at risk for a future depressive episode.

The following transition regimen is recommended to prevent recurrence of depressive episodes. The transition regimen entails increasing the dose of EPITEC to a maintenance stabilisation dose over six weeks following which other psychotropic and/or antiepileptic medicines can be withdrawn, if clinically indicated.
Since efficacy of EPITEC in mania has not been conclusively established, adjunctive therapy for the prevention of manic episodes should be considered.

**Recommended dose escalation to the maintenance total stabilisation dose for adults (over 18 years of age) treated for BIPOLAR DISORDER:**

**a. Adjunct therapy with enzyme inhibitors, e.g. valproate**

In patients who are receiving concomitant therapy with enzyme-inhibiting medicines, such as valproate, the initial EPITEC dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. In week 5 the dose should be escalated to 50 mg once a day or in two divided doses. Usually, the target dose to achieve optimal response is 100 mg/day given once a day or in two divided doses. However, depending on the patient's clinical response, the dose may be increased to a maximum of 200 mg per day.

**b. Adjunct therapy with enzyme inducers, e.g. carbamazepine and phenobarbitone, in patients NOT taking valproate**

In patients receiving concomitant therapy with enzyme-inducing medicines, such as carbamazepine or phenobarbitone and NOT taking valproate, the initial EPITEC dose is 50 mg once a day for two weeks. This is followed by 100 mg/day given in two divided doses for two weeks. In week 5 the dose should be increased to 200 mg/day administered as two divided doses. This dose may be further increased to 300 mg/day in week 6. Usually, the target dose to achieve optimal response is 400 mg/day administered in two divided doses, which may be given from week 7.

**c. Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine, e.g. lithium, bupropion, OR monotherapy with EPITEC**

The initial EPITEC dose in patients receiving concomitant therapy with medicines with no known/theoretical pharmacokinetic interaction with EPITEC, or who are receiving EPITEC in monotherapy, is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be escalated to 100 mg/day in week 5. Usually, the target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, in clinical trials, doses ranged from 100 – 400 mg.

**NOTE:** In patients who are receiving AEMs of which the pharmacokinetic interaction with EPITEC is not known, the dose escalation as recommended for EPITEC with co-administered valproate should be used.

The target stabilisation dose will alter depending on clinical response.

As soon as the target daily maintenance stabilisation dose has been achieved, other psychotropic medicines may be discontinued according to the dosage schedule outlined in the table below.

**Maintenance stabilisation total daily dose in BIPOLAR DISORDER following withdrawal of concomitant psychotropic or antiepileptic medicines**

<table>
<tr><th colspan="2">Treatment regimen</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards*</th></tr>
<tr><td colspan="2">a. Following withdrawal of enzyme inhibitors, e.g. valproate.</td><td>Double the stabilisation dose, not exceeding 100 mg/week, i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day.</td><td colspan="2">Maintain this dose (200 mg/day) (two divided doses).</td></tr>
<tr><td colspan="2" rowspan="3">b. Following withdrawal of enzyme inducers, e.g. carbamazepine, depending on original dose.</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td colspan="2">c. Following withdrawal of other psychotropic or antiepileptic medicines with no known clinical pharmacokinetic interaction with EPITEC, e.g. lithium, bupropion.</td><td colspan="3">Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100 – 400 mg).</td></tr>
<tr><td colspan="5">NOTE: In patients taking antiepileptic medicines where the pharmacokinetic interaction with EPITEC is currently not known, the dose escalation as recommended for EPITEC with concurrent valproate, should</td></tr>
</table>

| |
|---|
| be used. |
| *Dose may be increased to 400 mg/day as needed. |

**a. Following withdrawal of adjunct therapy with enzyme inhibitors such as sodium valproate**

EPITEC dosage should be increased to double the original target stabilisation dose and maintained at this, once valproate has been discontinued.

**b. Following withdrawal of adjunct therapy with enzyme inducers, e.g. carbamazepine, depending on original maintenance dose**

The dose of EPITEC should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

**c. Following withdrawal of adjunct therapy with other psychotropic or antiepileptic medicines with no known pharmacokinetic interaction with EPITEC, e.g. lithium or bupropion**

While the other medicine is being withdrawn, the target dose achieved in the dose escalation should be maintained throughout.

**Adjustment of EPITEC daily dosing in patients with BIPOLAR DISORDER following addition of other medicines**

There is no clinical experience with adjustment of daily EPITEC dose following the addition of other medicines. However, the following recommendations are based on the results of medicine interaction studies (see below):

**Adjustment of EPITEC daily dosing in patients with BIPOLAR DISORDER following the addition of other medicines**

<table>
<tr><th>Treatment regimen</th><th>Current EPITEC stabilisation dose (mg/day)</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards</th></tr>
<tr><td rowspan="3">a. Addition of enzyme inhibitors, e.g. valproate, depending on original dose of EPITEC.</td><td>200 mg</td><td>100 mg</td><td colspan="2">Maintain this dose (100 mg/day)</td></tr>
<tr><td>300 mg</td><td>150 mg</td><td colspan="2">Maintain this dose (150 mg/day)</td></tr>
<tr><td>400 mg</td><td>200 mg</td><td colspan="2">Maintain this dose (200 mg/day)</td></tr>
<tr><td rowspan="3">b. Addition of enzyme inducers, e.g. carbamazepine, in patients NOT taking valproate and depending on original dose of EPITEC.</td><td>200 mg</td><td>200 mg</td><td>300 mg</td><td>400 mg</td></tr>
<tr><td>150 mg</td><td>150 mg</td><td>225 mg</td><td>300 mg</td></tr>
<tr><td>100 mg</td><td>100 mg</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>c. Addition of other psychotropic or antiepileptic medicines with no known clinical pharmacokinetic interaction with EPITEC, e.g. lithium, bupropion.</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day) (range 100 – 400 mg).</td></tr>
<tr><td colspan="5">NOTE: In patients taking antiepileptic medicines where the pharmacokinetic interaction with EPITEC is currently not known, the dose escalation as recommended for EPITEC with concurrent valproate, should be used.</td></tr>
</table>

**Discontinuation of EPITEC in patients with bipolar disorder**

Abrupt cessation of therapy with EPITEC in clinical trials showed no increase in the incidence, severity or type of adverse events relative to placebo. Therefore, patients may discontinue treatment with EPITEC without a step-wise reduction of dose.

**Children (less than 18 years of age)**

Safety and efficacy of EPITEC in bipolar disorder have not been evaluated in children younger than 18 years of age. A dosage recommendation cannot be made.

**Special populations**

***Women taking hormonal contraceptives:***

***a. Starting EPITEC in patients already taking hormonal contraceptives***

The clearance of lamotrigine is increased when co-administered with an oral contraceptive combination, resulting in decreased lamotrigine levels. It is not recommended to adjust the dosage escalation guidelines for EPITEC based solely on the use of hormonal contraceptives. The recommended dosage escalation guidelines should be followed whether EPITEC is added to an inhibitor of lamotrigine glucuronidation, e.g. valproate, whether EPITEC is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbital, primidone or rifampicin; or whether EPITEC is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin.

***b. Starting hormonal contraceptives in patients already taking maintenance doses of EPITEC and NOT taking inducers of lamotrigine glucuronidation***

In most cases it will be necessary to increase the maintenance dose of EPITEC by as much as two-fold (see **section 4.4 and 4.5**).

***c. Stopping hormonal contraceptives in patients already taking maintenance doses of EPITEC and NOT taking inducers of lamotrigine glucuronidation***

According to the clinical response, it may be necessary to decrease the maintenance dose of EPITEC by as much as two-fold.

***Elderly (over 65 years of age)***

Since the pharmacokinetics of EPITEC in this age group do not differ significantly from a non-elderly population, no dosage adjustment from the recommended schedule is required.

***Hepatic impairment***

In general, initial, escalating and maintenance doses should be reduced by approximately 50 % in patients with moderate (Child-Pugh grade B) and 75 % in patients with severe (Child-Pugh grade C) liver impairment. Clinical response should dictate adjustments in escalation and maintenance doses.

***Renal impairment***

Caution is required when EPITEC is administered to patients with renal failure. For patients who suffer from end-stage renal failure initial doses of EPITEC should be based on the patient's antiepileptic regimen; however patients with significant renal functional impairment require reduced maintenance doses.

**Use with atazanavir/ ritonavir**

No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing atazanavir/ritonavir therapy.

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued.

Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see **section 4.5**).

**Paediatric population**

**Children aged less than 2 years**

EPITEC is contraindicated in children less than 2 years of age (see **section 4.3**).

**Method of administration**

Dose must be taken orally

## 4.3 CONTRAINDICATIONS

EPITEC is contraindicated in individuals with known hypersensitivity to lamotrigine or to any of the inactive ingredients in EPITEC.

Safety of EPITEC in pregnancy and lactation has not been established (see **section 4.6**).

In children younger than 2 years safety and efficacy have not been demonstrated.

## 4.4 Special warnings and precautions for use

Severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multi-organ dysfunction and disseminated intravascular coagulation, usually with fatal outcome. Similar cases have occurred in association with the use of EPITEC.

It is recommended that the medical practitioner closely monitor hepatic, renal and clotting parameters in patients receiving EPITEC.

Patients should be warned to see their doctor immediately if rashes or influenza-like symptoms associated with hypersensitivity develop. Withdrawal of EPITEC should be considered if any combination of unexplained rash, fever, flu-like symptoms, drowsiness or worsening of seizure control occurs within the first 8 weeks of treatment. Available data suggest that exceeding the recommended dose at the initiation of EPITEC therapy may be associated with an increased incidence of serious skin reactions requiring withdrawal of therapy.

Abrupt withdrawal of EPITEC may provoke rebound seizures. The risk may be reduced by tapering off withdrawal of EPITEC over a period of two weeks.

To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to bodyweight, do not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets (see **section 4.2**).

**Skin reactions**

There have been reports of adverse skin reactions, which have generally presented within the first 8 weeks after initiation of EPITEC treatment. Although the majority of rashes are mild and self-limiting, serious and potentially life-threatening skin rashes, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported, especially in children and in patients (adults and children) who used valproate concomitantly (see **section 4.8** and **4.4**). Isolated cases of skin reactions have occurred after prolonged treatment (6 months).

All clinical studies have reported skin reactions in approximately 10 % of adults and 17 % of children. Skin reactions occurred in 21 % of adults and in 34 % of children, who are on concomitant valproate. Of these, 12 % of adults and 17 % of children discontinued treatment.

Although some patients may experience irreversible scarring and there have been rare cases of associated death, the majority recover on medicine withdrawal.

The risk of serious skin rashes is higher in children than in adults. The incidence is estimated to be 1 in 1 000 (0,1 %) in adults, and in children between 1 in 100 to 1 in 300 require hospitalisation according to available data.

To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. Children's body weight should be monitored and the dose reviewed if necessary.

The initial presentation of a rash can be mistaken for an infection in children; medical practitioners should therefore consider the possibility of a medicine reaction in children that develop symptoms of fever and rash during the first eight weeks of EPITEC therapy.

Furthermore, the overall risk of skin reactions appears to be strongly associated with:

- High doses of EPITEC at the initiation of therapy and exceeding the recommended dose increases (see **section 4.2**).
- Concomitant valproate use, due to the fact that it increases the mean half-life of lamotrigine, as contained in EPITEC, nearly two-fold (see **section 5.2** and **4.2**).

All adults and children who develop a skin reaction should be promptly assessed and EPITEC discontinued immediately, as it cannot be reliably predicted which rashes will prove to be life-threatening, unless, of course, the rash is clearly not related to EPITEC.

Patients who have developed a rash due to EPITEC should not be re-challenged.

Rash has also been reported as part of a hypersensitivity syndrome. This syndrome is associated with a variable pattern of systemic symptoms including fever, pruritus, facial oedema, abnormalities of the blood and liver function, lymphadenopathy and

thrombocytopenia. Clinically this syndrome may vary across a wide spectrum of severity and may eventually lead to multi-organ failure and disseminated intravascular coagulation. It is important to note that patients may present with early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) even though rash is not evident. If a patient presents with the above signs and symptoms, he/she should be assessed immediately and EPITEC withdrawn if an alternative cause cannot be immediately established.

**Cardiac rhythm and conduction abnormalities**

It has been shown that lamotrigine, as contained in EPITEC, exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on these *in vitro* studies, EPITEC can slow ventricular conduction (widen QRS) and induce proarrhythmia, which can lead to sudden death, in patients with clinically important structural or functional heart disease (i.e., patients with heart failure, valvular heart disease, congenital heart disease, conduction system disease, ventricular arrhythmias, cardiac channelopathies [e.g., Brugada syndrome], clinically important ischemic heart disease, or multiple risk factors for coronary artery disease). Any expected or observed benefit of EPITEC in an individual patient with clinically important structural or functional heart disease must be carefully weighed against the risks for serious arrythmias and/or death for that patient.

Concomitant use of other sodium channel blockers may further increase the risk of proarrhythmia.

**Haemophagocytic lymphohistiocytosis (HLH)**

HLH has occurred in paediatric and adult patients taking EPITEC for various indications. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognised early and treated. Frequent findings include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, and liver function and coagulation abnormalities. In cases of HLH reported with EPITEC, patients have presented with signs of systemic inflammation (fever, rash, hepatosplenomegaly, and organ system dysfunction) and blood dyscrasias. Symptoms have been reported to occur within 8 to 24 days following the initiation of treatment. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. EPITEC should be discontinued if an alternative aetiology for the signs or symptoms cannot be established.

**Hormonal contraceptives**

***Effects of hormonal contraceptives on EPITEC efficacy***

Co-administration of combined oral contraceptive increases the clearance of lamotrigine leading to a reduction in lamotrigine levels (see **section 4.5**). Following titration, it may be necessary to increase maintenance doses of EPITEC (by as much as two-fold) to achieve maximal therapeutic response. In women taking a combined hormonal contraceptive that includes a “pill-free week” (one week of inactive treatment) and not

already taking an inducer of lamotrigine glucuronidation, gradual temporary increases in lamotrigine levels occurs during the week of inactive medicine.

When EPITEC dose increases are made before or during the week of inactive contraceptive medicine, increases in lamotrigine levels will be greater. Cases of breakthrough convulsions in women also using combined hormonal contraceptives, have been reported. For dosing instructions see **"General dosing recommendations in special patient populations"**, in **section 4.2**.

Women starting or stopping combined hormonal contraceptives during EPITEC therapy, should clinically be managed appropriately. Adjustments in EPITEC dosing may be needed. Other oral contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though lamotrigine pharmacokinetic parameters may similarly be affected.

***Effects of lamotrigine on hormonal contraceptive efficacy***

Studies have shown that there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH when lamotrigine, as in EPITEC, and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination (see **section 4.5**). The impact of these changes on ovarian ovulatory activity is unknown, however these changes may result in decreased contraceptive efficacy in patients taking combined hormonal contraceptive preparations. There have been reports of cases of unplanned pregnancy, metro/menorrhagia, breakthrough

bleeding and amenorrhoea. Therefore, patients should be advised to report changes in their menstrual pattern, i.e. breakthrough bleeding without delay.

**Dihydrofolate reductase**

There is a possibility of interference with folate metabolism during long-term therapy due to the fact that EPITEC is a weak inhibitor of dihydrofolate reductase.

**Renal failure**

Caution should be exercised in treating patients with renal failure because there is accumulation of the glucuronide metabolite (see **section 5.2: Special populations** and **section 4.2**).

**Bipolar disorder**

The possibility of a suicide attempt is inherent in bipolar disorder and close supervision of high-risk patients should accompany therapy.

There have been reports of suicidal ideation and behaviour in patients treated with antiepileptic medicines in several indications. A small increased risk of suicidal ideation and behaviour has been shown in antiepileptic medicines (AEM) trials. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine, as in EPITEC.

Patients should therefore be monitored for signs of suicidal ideation and behaviours and suitable treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour arise.

Worsening of depressive symptoms and/or the emergence of suicidality in patients with bipolar disorder may occur whether or not they are taking medicines for bipolar disorder, which includes EPITEC. Patients receiving EPITEC for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality. There may be a greater risk of suicidal thoughts or suicide attempts, especially in patients such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment and should receive careful monitoring during treatment.

In patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, changing the therapeutic regimen should be considered, which includes the possibility of discontinuing the medicine especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

**Epilepsy**

Abrupt cessation of therapy with EPITEC may provoke rebound seizures. The dose of EPITEC should be gradually reduced over a period of 2 weeks, unless safety concerns (e.g., rash) requires an abrupt withdrawal.

A clinically significant worsening of seizure frequency instead of improvement may be observed. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

EPITEC may aggravate myoclonic seizures**.**

**Exacerbation of Parkinsonian symptoms**

Reports have indicated that EPITEC may worsen Parkinsonian symptoms in patients with pre-existing Parkinson's disease, and there have been isolated reports of extrapyramidal effects and choreoathetosis in patients without Parkinson's disease.

**Lactose**

EPITEC contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance (e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption) should not take EPITEC.

EPITEC may have an effect on the glycaemic control of patients with diabetes mellitus.

**Paediatric population**

Efficacy may not be maintained in children taking lamotrigine, as in EPITEC, for the treatment of typical absence seizures.

## 4.5 Interaction with other medicines and other forms of interaction

Lamotrigine is metabolised by UDP-glucuronyl transferases. There is no evidence that lamotrigine, as contained in EPITEC, causes clinically significant inhibition or induction of hepatic medicine-metabolising enzymes and interactions between lamotrigine and medicines metabolised by cytochrome P450 enzymes are unlikely. Although EPITEC may induce its own metabolism, the effect is modest and unlikely to have any clinically significant consequences.

**Interactions involving antiepileptic medicines** (see **section 4.2**)

Antiepileptic medicines, such as phenytoin, carbamazepine, phenobarbitone and primidone induce hepatic medicine-metabolising enzymes. They halve the elimination half-life of EPITEC due to a significant increase in the metabolism of lamotrigine. Sodium valproate, alternatively, inhibits hepatic medicine-metabolising enzymes, thereby leading to a mean doubling of the elimination half-life of EPITEC, due to a significant reduction of the metabolism of lamotrigine.

A few patients demonstrated increases in plasma concentrations of other antiepileptic medicines; however, controlled trials provided no evidence that lamotrigine, as contained in EPITEC, affects the plasma concentrations of concomitant antiepileptic medicines. *In vitro* studies indicated that lamotrigine, as contained in EPITEC, does not displace other antiepileptic medicines from their protein binding sites.

Central nervous system events, including dizziness, ataxia, diplopia, blurred vision, and nausea, have been reported in patients who received carbamazepine following the introduction of EPITEC. Reducing the dose of carbamazepine usually leads to resolution of these adverse events.

The use of 200 mg lamotrigine, as in EPITEC, and 1200 mg oxcarbazepine were studied. Neither lamotrigine nor oxcarbazepine altered the metabolism of the other medicine. While carbamazepine halves the half-life of EPITEC, other doses of either medicine have not been studied.

According to a study the co-administration of felbamate (1200 mg twice daily) with lamotrigine, as in EPITEC (100 mg twice daily for 10 days), appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

The apparent clearance of lamotrigine by gabapentin appears to be unchanged after analysis of plasma levels in patients who received lamotrigine, as in EPITEC, both with and without gabapentin.

Clinical trials evaluated serum concentrations of levetiracetam and lamotrigine, assessing potential interactions between levetiracetam and lamotrigine, as in EPITEC. Data indicates that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

There are no pharmacokinetic interactions between lamotrigine and pregabalin. Steady-state trough plasma concentrations of lamotrigine, as in EPITEC, were not affected by concomitant administration of pregabalin (200 mg, 3 times daily).

Plasma concentrations of lamotrigine were unaffected by topiramate, however, administration of lamotrigine, as in EPITEC, resulted in a 15 % increase in topiramate concentrations.

**Interactions involving other psychotropic agents**

Co-administration of 100 mg/day EPITEC with lithium at a dose of 2 g of anhydrous lithium gluconate given twice daily for six days did not alter the pharmacokinetics of lithium.

Multiple oral doses of bupropion cause only a slight increase in the AUC of lamotrigine glucuronide and does not significantly affect the single dose pharmacokinetics of lamotrigine, as contained in EPITEC.

The formation of lamotrigine's primary metabolite, the 2-N-glucuronide, is minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol, or lorazepam *in vitro*. *In vitro* results further suggest that clearance of lamotrigine, as contained in EPITEC, is unlikely to be affected by clozapine, risperidone, sertraline or trazodone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100-400 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7 day period and continued once daily for a further 7

days. An average reduction of approximately 10 % in $C_{max}$ and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

**Interactions involving hormonal contraceptives**

***Effect of hormonal contraceptives on lamotrigine pharmacokinetics***

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination causes an increase in the clearance of lamotrigine of approximately two-fold, which results in reduced lamotrigine levels. After titration, it may be necessary to use higher maintenance doses of EPITEC (by as much as two-fold) to achieve maximal therapeutic response. A two-fold increase in EPITEC levels has been observed during the pill-free week and it is not possible to exclude dose-related adverse events. Contraception without a pill-free week should therefore be considered as first-line therapy (for example continuous hormonal contraceptives or non-hormonal methods) (see **section 4.2**).

***Effect of lamotrigine on hormonal contraceptives***

Clinical trial results have shown that lamotrigine, as contained in EPITEC, did not influence plasma concentrations of the ethinyloestradiol component following the administration of the combined oral contraceptive pill. A modest increase in oral

clearance of the levonorgestrel component was observed, resulting in an average 19 % and 12 % reduction in levonorgestrel AUC and $C_{max}$, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see **section 4.4**). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted. Cases of unplanned pregnancy, menstrual disorders and amenorrhoea have been reported. Patients should be advised to report any change in menstrual bleeding pattern to their medical practitioner, the same as with the introduction of any other chronic therapy in patients taking oral contraceptives.

**Interactions involving other medicines**

Studies have shown that due to induction of the hepatic enzymes responsible for glucuronidation, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life. In patients receiving concomitant therapy with rifampicin the treatment regimen recommended for EPITEC and concurrent glucuronidation inducers should be used (see **section 4.2**).

Plasma concentrations of lamotrigine, as in EPITEC, were approximately halved by lopinavir/ritonavir, most likely by means of induction of glucuronidation. In patients

receiving concomitant therapy with lopinavir/ritonavir, the appropriate treatment regimen should be used (see **section 4.2**).

Atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC of lamotrigine, as in EPITEC, on average by 32 % and $C_{max}$ by an average of 6 %, respectively (single 100 mg dose of lamotrigine). In patients receiving concomitant therapy with atazanavir/ ritonavir, the appropriate treatment regimen should be used (see **section 4.2**).

Lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. Data indicates that lamotrigine is a more potent *in vitro* inhibitor of OCT 2 than cimetidine. Renally excreted medicines (e.g. metformin, gabapentin and varenicline), which are substrates of OCT 2 co-administered with lamotrigine, as in EPITEC, may result in increased plasma levels of these medicines.

**Laboratory tests**

Lamotrigine, as in EPITEC, has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false-positive readings, particularly for phencyclidine (PCP). A more specific analytical method should be used to confirm a positive result.

## 4.6 Fertility, pregnancy and lactation

Safety of EPITEC in pregnancy and lactation has not been established. EPITEC use is contraindicated during pregnancy (see **section 4.3**).

**Pregnancy**

There is evidence that there is substantial increase in the risk for major congenital malformations, including oral clefts from data on pregnant women exposed to lamotrigine, as in EPITEC, monotherapy during the first trimester of pregnancy.

**Breastfeeding**

Women on treatment with Epitec should not breastfeed their infants.

Lamotrigine has been reported to pass into breast milk in highly variable concentrations. As a result, serum concentrations of lamotrigine may reach levels at which pharmacological effects can occur. Total lamotrigine, as in EPITEC, levels in infants of up to approximately 50 % of the mother's levels were seen in some breastfed infants.

**Fertility**

Animal experiments did not reveal impairment of fertility by lamotrigine, as in EPITEC.

## 4.7 Effects on the ability to drive and use machines

EPITEC may cause adverse events of a neurological character, such as dizziness and diplopia. Patients should therefore be advised to see how EPITEC affects them before they drive or operate machinery.

## 4.8 Undesirable effects

**EPILEPSY**

**Blood and lymphatic system disorders**

*Frequent*: Blood dyscrasia.

*Less frequent:* Haematological abnormalities, including anaemia, neutropenia, leucopenia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis, lymphadenopathy.

Haematological abnormalities may or may not be associated with a hypersensitivity syndrome (see **section 4.4**).

**Immune system disorders**

*Less frequent:* Hypersensitivity syndrome. Rash has also been reported as part of a hypersensitivity syndrome. This syndrome is associated with a variable pattern of systemic symptoms, which may include fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome demonstrates a wide spectrum of clinical severity and in rare cases may cause disseminated intravascular coagulation and multi-organ failure. It is important to note that early hypersensitivity manifestations (such as fever, lymphadenopathy) may be present even though rash is not evident. If the patient demonstrates such signs and symptoms, he/she should be evaluated immediately and EPITEC discontinued if an alternative aetiology cannot be established (see **section 4.4**).

**Psychiatric disorders**

*Frequent*: Irritability.

*Less frequent:* Aggression, tics, hallucinations, confusion.

**Nervous system disorders**

*Frequent*: Dizziness, somnolence, headache, unsteadiness, tiredness, irritability/aggression, depression, tremor, vertigo, paraesthesia, insomnia, ataxia, agitation, and confusion.

*Less frequent*: Hallucinations, nystagmus, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, and an increase in seizure frequency.

**Eye disorders**

*Frequent*: Diplopia, blurred vision.

*Less frequent*: *C*onjunctivitis.

**Gastrointestinal disorders**

*Frequent*: Nausea, vomiting, gastrointestinal disturbance (including vomiting and diarrhoea).

**Hepatobiliary disorders**

*Less frequent*: Increased liver function tests, hepatic dysfunction, hepatic failure.

Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.

**Skin and subcutaneous tissue disorders**

*Frequent*: Skin rash.

*Less frequent:* Stevens-Johnson syndrome, toxic epidermal necrolysis.

Skin rashes, usually maculopapular in appearance, may occur within 8 weeks of starting treatment and resolves on withdrawal of EPITEC. Severe skin reactions, including angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported (see **section 4.4**). The majority recover on cessation of EPITEC therapy, but some patients experience irreversible scarring and there have been rare instances of associated death.

It appears that the overall risk of rash is strongly associated with high initial doses of EPITEC and with exceeding the recommended dose escalation (see **section 4.2**).

Rash has also occurred as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see **section 4.4**).

**Musculoskeletal, connective tissue and bone disorders**

*Less frequent:* Lupus-like reactions.

**General disorders and administrative site conditions**

*Frequent* Tiredness.

**BIPOLAR MOOD DISORDER**

For an overall safety profile of EPITEC the following adverse events should be considered alongside those seen in patients with epilepsy:

**Skin and subcutaneous tissue disorders**

*Frequent:* Skin rash

*Less frequent:* Stevens-Johnson syndrome

**Nervous system disorders**

*Frequent:* Headache, agitation, somnolence, dizziness.

**Musculoskeletal, connective tissue and bone disorders**

*Frequent:* Arthralgia.

**General disorders and administrative site disorders**

*Frequent:* Pain, back pain.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8 or drugsafetysa@cipla.com

### 4.9 Overdose

**Symptoms and signs:** Ingestion of doses in excess of 10 – 20 times the maximum therapeutic dose has been reported and overdose resulted in symptoms which includes nystagmus, ataxia, impaired consciousness, grand mal convulsions, and coma.

**Treatment:** The patient should be admitted to hospital and given appropriate supportive therapy, if an overdosage has occurred. Gastric lavage should be done.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A. 2.5 Antiepileptics

*In vitro* pharmacological studies suggest that lamotrigine blocks voltage-sensitive sodium channels, thereby stabilising neuronal membranes and inhibiting the presynaptic release of neurotransmitters, principally glutamate. Glutamate, an excitatory amino acid, is thought to play a key role in the generation of epileptic seizures. Lamotrigine may also directly inhibit high-frequency sustained repetitive firing of sodium-dependent action potentials.

## 5.2 Pharmacokinetic properties

Lamotrigine is well absorbed from the gastrointestinal tract. Peak plasma concentrations have been reported 2,5 hours after oral administration. It is widely distributed in the body and is reported to be about 55 % bound to plasma proteins. Lamotrigine is extensively metabolised in the liver and excreted almost entirely in urine, principally as a glucuronide conjugate. It slightly induces its own metabolism and the half-life at steady state is reported to be 24 hours. The half-life is affected by the concomitant administration of other antiepileptic medicines, and is generally shorter in children than in adults. The half-life of lamotrigine increases to approximately 59 hours when co-administered with sodium valproate alone.

**Special populations**

***Elderly***

Clearance of lamotrigine does not differ to a clinically relevant extent between young and elderly patients.

***Renal impairment***

Clearance and half-life of lamotrigine is reduced and prolonged, respectively, in patients with functional renal impairment. While initial doses of lamotrigine should be based on the patient's antiepileptic medicine regimen, reduced maintenance doses should be used in patients with significant renal functional impairment (see **section 4.2**).

***Hepatic impairment***

Clearance of lamotrigine is reduced in patients with hepatic impairment and reduced doses should generally be used in patients with grade B or C (Child-Pugh Classification) hepatic impairment (see **section 4.2**).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate,

magnesium stearate,

maize starch,

microcrystalline cellulose,

sodium starch glycolate and

yellow oxide of iron

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store at or below 25 ºC, in a dry place.

Keep the blister strips in the outer carton until required for use.

## 6.5 Nature and contents of container

Colourless PVC and aluminium foil blister strips of 10 tablets, packed in 60's (this applies to all 4 strengths).

## 6.6 Special precautions for disposal and other handling

No special requirements

# 7 HOLDER OF CERTIFICATE OF REGISTRATION

**CIPLA MEDPRO (PTY) LTD.**

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Mispel Street

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7530

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# 8 REGISTRATION NUMBER(S)

EPITEC 25: A38/2.5/0571

EPITEC 50: A38/2.5/0572

EPITEC 100: A38/2.5/0573

EPITEC 200: A38/2.5/0574

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 March 2005

## 10 DATE OF REVISION OF THE TEXT

07 January 2022