PROFESSIONAL INFORMATION FOR

EPITEC 25 / 50 / 100 / 200 TABLETS

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

EPITEC 25 mg, tablets

EPITEC 50 mg, tablets

EPITEC 100 mg, tablets

EPITEC 200 mg, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EPITEC 25: Each tablet contains lamotrigine 25 mg.

Contains sugar: lactose monohydrate 52,50 mg per tablet.

EPITEC 50: Each tablet contains lamotrigine 50 mg.

Contains sugar: lactose monohydrate 105,50 mg per tablet.

EPITEC 100: Each tablet contains lamotrigine 100 mg.

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

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 adolescents (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**).

General Dosing Recommendations:

Administration:

If a calculated dose of EPITEC (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets, the dose to be administered should be 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 dosage 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 lamotrigine 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.

Dosage in epilepsy monotherapy: Monotherapy: Adults and adolescents (over 12 years)

The initial dose of EPITEC in monotherapy is 25 mg once a day for 2 weeks, followed by 50 mg once a day for 2 weeks. Thereafter dosage should be increased by maximum of 50 to 100 mg every 1 to 2 weeks until optimal response is achieved.

The usual maintenance dose to achieve optimal response is 100 to 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.

Dosage in epilepsy add-on therapy:

Adults and adolescents (over 12 years of age):

Patients taking concomitant anitiepilectic medicines

In patients taking concomitant antiepileptic medicines or other medicines (see **section 4.5**) that induce lamotrigine glucuronidation with/without other antiepileptic medicines (except valproate), the initial EPITEC dose is 50 mg once a day 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 to 2 weeks until optimal response is achieved.

The usual maintenance dose to achieve optimal response is 200 to 400 mg/day administered in 2 divided doses.

Patients taking sodium valproate

In patients taking sodium valproate, with or without any other antiepileptic medicines, the initial EPITEC dose is 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 to 50 mg every 1 to 2 weeks until optimal response is achieved.

The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or in 2 divided doses. Do not exceed recommended initial dose.

Patients taking oxcarbazepine

In 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 to 100 mg every 1 to 2 weeks until optimal response is achieved or a dose of 200 mg is reached.

The usual maintenance dose to achieve an optimal response is 100 to 200 mg/day once a day or as two divided doses.

Table 1: Recommended treatment regimen for adults and adolescents over 12 years of age

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Maintenance Dose
Monotherapy	25 mg (once a day)	50 mg (once a day)	100-200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks

Add-on therapy with valproate regardless of any concomitant medicines		12,5 mg (given as 25 mg alternate on days)	25 mg (once a day)	100-200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25-50 mg every 1-2 weeks
Add-on therapy without valproate	This dosage regimen should be used with: phenytoin, carbamazepine, phenobarbitone, primidone, or with other inducers of lamotrigine glucuronidation (see **section 4.5**).	50 mg (once a day)	100 mg (two divided doses)	200-400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1-2 weeks

Treatment regimen		**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance Dose**
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	25 mg (once a day)	50 mg (once a day)	100-200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks
In patients taking antiepileptic medicines where the pharmacokinetic interaction with lamotrigine is currently not known (see **section 4.5**), the treatment regimen as recommended for EPITEC with concurrent valproate should be used.				

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 to 12 years:

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 should be equal to the lower number of whole tablets.

Patients taking antiepileptic medicines

In 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:

The initial EPITEC dose is 0,6 mg/kg body mass per day in 2 divided doses for 2 weeks, followed by 1,2 mg/kg/day for 2 weeks. Thereafter the dose should be increased by a maximum 1,2 mg/kg every 1 to 2 weeks until optimal response is achieved.

The usual maintenance dose to achieve optimal response is 5 to 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):

In patients taking sodium valproate with/without any other AEMs, the initial EPITEC dose is 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 to 2 weeks until optimal response is achieved.

The usual maintenance dose to achieve optimal response is 1 to 5 mg/kg/day once daily or in 2 divided doses. Maximum daily dose of 200 mg should not be exceeded.

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 to 2 weeks until optimal response is achieved or a dose of 200 mg is reached.

The usual maintenance dose to achieve optimal response is 1 to 10 mg/day given once a day or as two divided doses, with a maximum of 200 mg/day.

Table 2: Recommended *treatment regimen* for children aged 2-12 years (total daily dose in mg/kg bodyweight/day) **

Treatment regimen		**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance Dose**
Add-on therapy with valproate regardless of any other concomitant medicine		0,15 mg/kg* (once a day)	0,3 mg/kg (once a day)	0,3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
Add-on therapy without valproate	This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone, or with other inducers of lamotrigine glucuronidation (see **section 4.5**).	0,6 mg/kg (two divided doses)	1,2 mg/kg (two divided doses)	1,2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day.
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	0,3 mg/kg (one or two divided doses)	0,6 mg/kg (one or two divided doses)	0,6 mg/kg increments every one to two weeks to achieve a maintenance dose of 1-10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
In patients taking AEMs where the pharmacokinetic interaction with lamotrigine is currently not known (see **section 4.5),** the treatment regimen as recommended for EPITEC with concurrent valproate should be used.				

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Maintenance Dose
* If the calculated daily dose in patients taking valproate is 1-2 mg, then 2 mg EPITEC may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg, then EPITEC should not be administered. ** If the calculated dose of EPITEC cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet			

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

Patients aged 2-6 years may require a maintenance dose at the higher end of the recommended range.

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.

Children aged less than 2 years:

EPITEC has not been studied as monotherapy in children less than 2 years of age or as add-on therapy in children less than 1 month of age. The safety and efficacy of EPITEC as add-on therapy of partial seizures in children aged 1 month to 2 years has not been established. Therefore, EPITEC is not recommended in children less than 2 years of age.

BIPOLAR DISORDER

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

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 (**see Table 3**) following which other psychotropic and/or antiepileptic medicines can be withdrawn, if clinically indicated. (**See Table 4**)

Table 3: Recommended dose escalation to the maintenance total stabilisation dose for adults (over 18 years of age) treated for BIPOLAR DISORDER:

a. **Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate**

   In patients taking glucuronidation inhibiting concomitant 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, the dose may be increased to a maximum of 200 mg per day, depending on the patient's clinical response.

b. **Adjunct therapy inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate. This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other medicines**

known to induce lamotrigine glucuronidation, including liponavir/ritonavir (see section 4.5):

In patients currently taking medicines that induce lamotrigine glucuronidation 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. The usual target dose to achieve optimal response is 400 mg/day administered in two divided doses, which may be given from week 7.

Monotherapy with lamotrigine OR Adjunctive therapy in patients taking other medicines that do not significantly induce or inhibit lamotrigine glucuronidation (see section 4.5): The initial EPITEC dose 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. The usual 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 to 400 mg.

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Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medicines may be discontinued according to the dosage schedule outlined in the table 4 below.

Table 4 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 medicines that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)</td><td colspan="3">Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100 to 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>
<tr><td colspan="5">*Dose may be increased to 400 mg/day as needed.</td></tr>
</table>

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 inducers of lamotrigine glucuronidation, depending on original maintenance dose. This regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone or other medicines known to induce lamotrigine glucuronidation (see section 4.5):**

   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**

   The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medicine.

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 Table 5):

Table 5: Adjustment of EPITEC daily dosing in patients with BIPOLAR DISORDER following the addition of other medicines

<table>
<tr><th colspan="2">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 colspan="2" rowspan="3">a. Addition of lamotrigine glucuronidation 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 colspan="2" rowspan="3">b. Addition of lamotrigine glucuronidation inducers, in patients NOT taking valproate and depending on original dose of EPITEC. This dosage regimen should be used with: phenytoin, carbamazepine, phenobarbitone, primodone or with other indicers of lamotrigine glucuronidation</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 colspan="2">c. Addition of other medicines that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day) (range 100 to 400 mg).</td></tr>
<tr><td colspan="6">NOTE: In patients taking antiepileptic medicines where the pharmacokinetic interaction with EPITEC is currently not known, the treatment regimen as recommended for EPITEC with concurrent valproate, should be used.</td></tr>
</table>

Discontinuation of EPITEC in patients with bipolar disorder

In clinical trials, there was no increase in the incidence, severity or type of adverse experiences following abrupt termination of EPITEC versus placebo. Therefore, patients may discontinue treatment with EPITEC without a step-wise reduction of dose.

Children and adolescents (less than 18 years of age)

EPITEC is not indicated for use in bipolar disorder in children and adolescents aged less than 18 years (see **section 4.4**). 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

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see **section 4.4** and **4.5**), no adjustments to the recommended dose escalation guidelines for EPITEC should be necessary solely based on the use of hormonal contraceptives. The recommended dosage escalation guidelines should be followed whether EPITEC is added to valproate (an inhibitor of lamotrigine glucuronidation) or to an inducer of lamotrigine glucuronidation, or whether EPITEC is added in the absence of valproate or an inducer of lamotrigine glucuronidation (see Table 1 for epilepsy and Table 3 for bipolar patients).

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**).

It is recommended that from the time that the hormonal contraceptive is started, the EPITEC dose is increased by 50-100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases.

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

The maintenance dose of EPITEC will in most cases need to be decreased by as much as 50 % (see **section 4.4** and **4.5**). It is recommended to gradually decrease the daily dose of EPITEC by 50-100 mg each week (at a rate not exceeding 25 % of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise.

Use with atazanavir / ritonavir:

Although atazanavir / ritonavir has been shown to reduce lamotrigine plasma concentrations (see **section 4.5**), no adjustments to the recommended dose escalation guidelines for EPITEC should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the recommended guidelines based on whether EPITEC is added to valproate (an inhibitor of lamotrigine

glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether EPITEC is added in the absence of valproate or an inducer of lamotrigine glucuronidation.

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

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.

4.3 Contraindications

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

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 who acutely develop any combination of unexplained rash, fever, flu-like symptoms, drowsiness or worsening of seizure control, especially within the first month of starting treatment with 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, in patients with epilepsy. Unless safety concerns (e.g. rash) require an abrupt withdrawal, the dose of EPITEC should be gradually decreased 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 (SJS), 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 the majority recover on withdrawal of EPITEC, some patients experience irreversible scarring and there have been cases of associated death. In adults enrolled in studies utilising the current EPITEC dosing recommendations, the incidence of serious skin rashes is approximately 1 in 500 in epilepsy patients. Approximately half of these cases have been reported as SJS (1 in 1000).

The risk of serious skin rashes is higher in children than in adults. Available data suggest the incidence of rashes which needed hospitalisation in children is from 1 in 300 to 1 in 100. In clinical trials with EPITEC in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1000. 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**).

Caution is also required when treating patients with a history of allergy or rash to other antiepileptic medicines, as the frequency of non-serious rash after treatment with EPITEC was approximately three times higher in these patients than in those without

such history.

As it cannot be predicted reliably which rashes will prove to be life-threatening, all patients (adults and children) who develop a rash should be promptly evaluated and EPITEC withdrawn immediately unless the rash is clearly not related to EPITEC treatment. It is recommended that EPITEC not be restarted in patients who have discontinued due to rash associated with prior treatment with EPITEC.

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, pruritis, facial oedema, abnormalities of the blood, liver, and kidney aseptic meningitis and thrombocytopenia. The syndrome shows a wide spectrum of clinical severity and may lead to disseminated intravascular coagulation and multi-organ failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately, and EPITEC discontinued if an alternative aetiology cannot be immediately established.

Aseptic meningitis was reversible on withdrawal of the EPITEC in most cases but recurred in a number of cases on re-exposure to EPITEC. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. EPITEC should not be restarted in patients who have discontinued due to aseptic meningitis associated with treatment of EPITEC.

Caution is also required when treating patients with a history of allergy or rash to other AEMs as the frequency of non-serious rash after treatment with lamotrigine was

approximately three times higher in these patients than in those without such history.

HLA-B*1502 allele in individuals of Asian (primarily Han Chinese and Thai) origin has been shown to be associated with the risk of developing SJS/TEN when treated with lamotrigine. If these patients are known to be positive for HLA-B*1502, use of lamotrigine should be carefully considered.

Haemophagocytic lymphohistiocytosis (HLH)

HLH has occurred in patients taking EPITEC (see **section 4.8**). HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation.

Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. EPITEC should be discontinued unless an alternative aetiology can be established.

Clinical worsening and suicide risk:

There is evidence that patients with bipolar disorder and with epilepsy, have an elevated risk for suicidality. This risk may continue during treatment.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines (AEMs), including EPITEC in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomised placebo-controlled trials of AEMs

(including EPITEC) has also shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

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

Patients receiving EPITEC for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain 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, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing EPITEC, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Hormonal contraceptives

Effects of hormonal contraceptives on EPITEC efficacy

An ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination has been demonstrated to increase the clearance of EPITEC by approximately two-fold resulting in decreased EPITEC levels (see **section 4.5**). Following titration, higher maintenance doses of EPITEC (by as much as two-fold) will be needed in most cases to attain an optimum 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 EPITEC 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.

Effect of EPITEC on organic cationic transporter 2 (OCT 2) substrates

Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins (see **section 4.5**). This may result in increased plasma levels of certain medicines that are substantially excreted via this route. Co-administration of EPITEC with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

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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. However, during prolonged human dosing of up to 1 year, EPITEC did not induce significant changes in haemoglobin concentration, mean corpuscular volume, serum or red blood cell folate concentrations.

Renal failure

In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. 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**).

Brugada-type ECG

A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using lamotrigine in patients with Brugada syndrome.

Cardiac rhythm and conduction abnormalities

In vitro testing showed that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on these in vitro findings, lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia in patients with clinically important structural or functional heart disease. Therefore, any expected or observed benefit of lamotrigine for those patients must be carefully weighed

against the potential risks for serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risk of proarrhythmia (see **section 5.1).**

Bipolar disorder

Children and adolescents (less than 18 years of age):

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders. EPITEC should not be used in children and adolescents with bipolar disorder.

Effects on Ability to Drive and Use Machines:

In clinical trials with EPITEC adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how EPITEC therapy affects them before driving or operating machinery.

Excipient warnings:

EPITEC tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take EPITEC tablets (see **section 2**)**.**

4.5 Interaction with other medicines and other forms of interaction

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Medicines that induce or inhibit

glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs, may also enhance the metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce its own metabolism, but the effect is modest and unlikely to have significant clinical consequences.

Those medicines that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in Table below. Specific dosing guidance for these medicines is provided in **section 4.2**. In addition, this table lists those medicines which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such medicines would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine..

Effects of medicines on the concentration of lamotrigine):

Medicines that increase the concentration of lamotrigine (doubling of lamotrigine half-life)	**Medicines that decrease the concentration of lamotrigine (halving lamotrigine half-life)**	**Medicines have little or no that effect on the concentration of lamotrigine**
Valproate	Atazanavir/ritonavir*	Aripiprazole
	Carbamazepine	
	Ethinyloestradiol/levonorgestrel combination **	Bupropion
	Phenytoin	Felbamate
	Phenobarbitone	Gabapentin
	Phenytoin	Oxcarbazepine
	Primidone	
	Rifampicin	Lacosamide
		Levetiracetam
		Lithium
		Olanzapine

		Oxcarbazepine Paracetamol Perampanel Topiramate Pregabalin Zonisamide
* For dosing guidance, see **section 4.2** - General Dosing Recommendations for EPITEC in Special Patient Populations, plus for women taking hormonal contraceptives also see **section 4.4** – Hormonal Contraceptives.		

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

Valproate, which inhibits the glucuronidation of lamotrigine, significantly reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.

Certain AEMs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, significantly enhance the metabolism of lamotrigine leading to a halving of the elimination half-life of EPITEC..

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.

In a study in healthy adult volunteers using doses of 200 mg lamotrigine and 1 200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine. However, other doses of

either medicine have not been studied, while carbamazepine halves the EPITEC half-life (see above).

In a study of health volunteers, 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.

In a study of patients with epilepsy, co-administration of zonisamide (200 to 400 mg/day) with EPITEC (150 to 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10 %.

Although increases in the plasma concentrations of other antiepileptic medicines have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant antiepileptic medicines. Evidence from *in vitro* studies indicates that lamotrigine does not displace other antiepileptic medicines from protein binding sites**.**

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.

In a study in healthy adult volunteers, 15 mg olanzapine reduced the AUC and C_{max} of lamotrigine by an average of 24 % and 20 %, respectively. EPITEC at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of EPITEC 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 EPITEC, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone and none when EPITEC was administered alone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100 to 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.

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.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of EPITEC (≥ 100 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.

In vitro inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol, or lorazepam. Bufuralol

metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of medicines eliminated predominantly by CYP2D6. Results of in vitro experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

The use of an ethinyloestradiol/levonorgestrel (30 mcg/150 mcg) 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**). General Dosing Recommendations for EPITEC in Special Patient Populations (for dosing instructions for women taking hormonal contraceptives) and Special warnings and precautions for use).

Breakthrough seizures have been reported in women using contraceptives.

Effect of lamotrigine on hormonal contraceptives pharmacokinetics:

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.

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** - General Dosing Recommendations for EPITEC in Special Patient Populations).

In a study in healthy adult volunteers, paracetamol 1g (four times daily) reduced the plasma AUC and C_{min} of lamotrigine by an average of 20 % and 25 %, respectively.

In a study in healthy adult volunteers, paracetamol 1g (four times daily) reduced the plasma AUC and C_{min} of lamotrigine by an average of 20 % and 25 %, respectively.

Data from *in vitro* assessment of the effect of lamotrigine at OCT 2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with IC_{50} values of 53,8 µM (see **section 4.4)**.

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 alternative chemical method should be used to confirm a positive result.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of EPITEC in pregnancy and lactation has not been established.

Use during pregnancy:

There is some evidence of an increased risk of oral cleft malformations following exposure to EPITEC in pregnancy.

The decision to use EPITEC during pregnancy should be taken by the physician following assessment of the benefit / risk profile.

A large amount of data on pregnant women exposed to EPITEC monotherapy during the first trimester of pregnancy (more than 8700) do not suggest a substantial increase in the risk for major congenital malformations, including oral clefts. Animal studies have shown developmental toxicity (see **section 5.3**).

If therapy with EPITEC is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels. Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine plasma levels during pregnancy with a potential risk of loss of seizure control. After birth, lamotrigine levels may increase rapidly with a risk of dose-related adverse events. Therefore lamotrigine serum concentrations should be monitored before, during and after pregnancy, as well as shortly after birth. If necessary, the dose should be adapted to

maintain the lamotrigine serum concentration at the same level as before pregnancy or adapted according to clinical response. In addition, dose-related undesirable effects should be monitored after birth.

Breastfeeding

The decision to breastfeed should be taken by the mother in consultation with the physician. The potential benefits of breastfeeding should be weighed against the potential risk of adverse effects occurring in the infant.

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50 % of the mothers'. Therefore, in some breastfed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

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

Frequent: Skin rash

Less Frequent: Stevens-Johnson syndrome

Frequency unknown: T**oxic epidermal necrolysis**

As reported in clinical trials, skin rashes occurred in up to 10 % of patients taking EPITEC and in 5 % of patients taking placebo. The skin rashes led to the withdrawal of EPITEC treatment in 2 % of patients. The rash, usually maculopapular in appearance, generally appears within 8 weeks of starting treatment and resolves on withdrawal of lamotrigine (see **section 4.4**).

Serious, potentially life-threatening skin rashes, including angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Although the majority recover on withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see **section 4.4)**.

The overall risk of rash appears to be strongly associated with high initial doses of EPITEC and exceeding the recommended dose escalation of EPITEC therapy (see **section 4.2**).

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see **section 4.4**).

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 DRESS / hypersensitivity syndrome (see **section 4.4**).

Frequency Unkown: Pseudolymphoma.

Immune system disorders

Less frequent: DRESS / Hypersensitivity syndrome* including such symptoms as fever, lymphadenopathy, facial oedema, abnormailities of the blood, liver, and kidney. *Rash has also been reported as part of a hypersensitivity syndrome which shows 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:	Aggression, irritability
Less frequent:	Aggression, Tics **(motor and/or phonic tics)**, hallucinations, confusion

Nervous system disorders

Very common:	Headache
Common:	Dizziness, somnolence, tiredness, tremor, vertigo, paraesthesia, insomnia
Uncommon:	Ataxia
Rare:	Nystagmus

Eye disorders

Uncommon:	Diplopia, blurred vision

Gastrointestinal disorders

Common:	Nausea, vomiting. diarrhoea

Hepatobiliary disorders

Very rare:	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.

Musculoskeletal, connective tissue and bone disorders

Very rare: Lupus-like reactions

General disorders and administrative site conditions

Common: 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

Very common: Skin rash

Rare: Stevens-Johnson syndrome

When all bipolar disorder studies (controlled and uncontrolled) conducted with EPITEC are considered, skin rashes occurred in 12 % of patients on EPITEC. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8 % of patients taking EPITEC and in 6 % of patients taking placebo.

Nervous system disorders

Very common: Headache

Common: Agitation, somnolence, dizziness

Musculoskeletal, connective tissue and bone disorders

Common: Arthralgia

General disorders and administrative site disorders

Common: Pain, back pain

Post-marketing data:

Blood and lymphatic system disorders: Haemophagocytic lymphohistiocytosis (see **section 4.4**)

Immune system disorders: Hypogammaglobulinaemia

Skin and subcutaneous disorders: Alopecia

Psychiatric disorders: Nightmares

Nervous system disorders: Somnolence, headache, ataxia, dizziness, nystagmus, tremor, insomnia, aseptic meningitis (see **section 4.4**), agitation, unsteadiness, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, and in epilepsy only, increase in seizure frequency.

EPITEC may worsen Parkinsonian symptoms in patients with pre-existing Parkinson's disease and reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye disorders: Conjunctivitis

Renal and Urinary disorders: Tubulointerstitial nephritis*

* may occur in association with uveitis

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 "Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

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

broadening (intraventricular conduction delay) has also been observed in overdose patients (see **section 4.8**).

Treatment: In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated, taking into account potential effects on cardiac conduction (see **section 4.4**). **Use of intravenous lipid therapy may be considered for treatment of cardiotoxicity that responds insufficiently to sodium bicarbonate.** There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see **section 5.2**).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 2.5 Anticonvulsants including antiepileptics

Pharmacotherapeutic group: Antiepileptics, Other antiepileptics

ATC code: **N03AX09** **https://www.whocc.no/atc_ddd_index/?code=N03AX09**

In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow

ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia.

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.

5.2 Pharmacokinetic properties

In healthy fasting young adult volunteers, lamotrigine is completely absorbed from the gut. The peak plasma concentration occurs 2,5 hours after oral administration. The mean elimination half-life is 29 hours, and the pharmacokinetic profile is linear up to 450 mg, the highest single dose tested. The half-life of lamotrigine is decreased by concomitant medicine with a mean value of approximately 14 hours when given with enzyme-inducing medicines such as carbamazepine and phenytoin and increased to a mean of approximately 70 hours when co-administered with sodium valproate alone (see **section 4.2**). Following multiple administrations of lamotrigine (150 mg twice daily) to normal volunteers, there is modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state. Lamotrigine is 55 % bound to plasma proteins. Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults, with the highest values in children under 5 years. The half-life

of lamotrigine is generally shorter in children than in adults, with a mean value of approximately 7 hours when given with enzyme-inducing medicines such as carbamazepine and phenytoin. The half-life of lamotrigine increases to mean values of approximately 45 to 55 hours when co-administered with sodium valproate alone (see **section 4.2**).

Special populations

Elderly

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

After single doses, apparent clearance decreased by 12 % from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10 %, from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0,39 mL/min/kg) lies within the range of the mean clearance values (0,31 to 0,65 mL/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg.

Renal impairment

12 volunteers with chronic renal failure and another 6 individuals undergoing hemodialysis were each given a single 100 mg dose of lamotrigine. Mean CL/F were 0,42 mL/min/kg (chronic renal failure), 0,33 mL/min/kg (between haemodialysis) and 1,57 mL/min/kg (during haemodialysis) compared to 0,58 mL/min/kg in healthy

volunteers. Mean plasma half-lives were 42,9 hours (chronic renal failure), 57,4 hours (between haemodialysis) and 13,0 hours (during haemodialysis), compared to 26,2 hours in healthy volunteers. On average, approximately 20 % (range = 5,6 to 35,1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on patients' anti-epileptic medicine (AEM) regimen; reduced maintenance doses should be used in patients with significant renal functional impairment (see **section 4.2**). 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

A single-dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as control. The median apparent clearance of lamotrigine was 0,31; 0,24 or 0,10 mL/min/kg in patients with grade A, B, or C (Child–Pugh Classification) hepatic impairment, respectively, compared to 0,34 mL/min/kg in the healthy controls. 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

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

Patient ready packs, closures, wadding, desiccant.

Clear, colouless, transparent non-toxic PVC film/printed aluminium foil blister strips of 10 tablets packed in 60’s in a carton.

(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.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer care number: 080 222 6662

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

Namibia: NS2

EPITEC 25: 06/2.5/0092

EPITEC 50: 06/2.5/0091

EPITEC 100: 06/2.5/0090

EPITEC 200: 06/2.5/0089

Botswana: S2

EPITEC 25: BOT0700978

EPITEC 50: BOT0700977

EPITEC 100: BOT0700976

EPITEC 200: BOT0700975

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation:18 March 2005

Latest renewal: Not applicable

10 DATE OF REVISION OF THE TEXT

22 July 2024.