Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lamotrigine PTR Pharma 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg lamotrigine.

Excipient with known effect
Each tablet contains 136 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round (8 mm in diameter), flat tablet with a break-mark on one side and "5" embossed on the other side.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

Adults and adolescents aged 13 years and above

- Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.
- Seizures associated with Lennox-Gastaut syndrome. Lamotrigine PTR Pharma is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.

Children and adolescents aged 2 to 12 years

- Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.
- Monotherapy of typical absence seizures.

Bipolar disorder

Adults aged 18 years and above

- Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

Lamotrigine PTR Pharma is not indicated for the acute treatment of manic or depressive episodes.

4.2 Posology and method of administration

Posology
Lamotrigine PTR Pharma should be swallowed whole, halved (both strengths) or quartered (only 100 mg), and should not be chewed or crushed.

If the calculated dose of lamotrigine (for example for treatment of children with epilepsy or patients with hepatic impairment) does not equate to whole or halved tablets, the dose to be administered is that equal to the lower number of whole or halved tablets.

Restarting therapy

Prescribers should assess the need for escalation to maintenance dose when restarting Lamotrigine PTR Pharma in patients who have discontinued Lamotrigine PTR Pharma for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see section 4.4). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing lamotrigine exceeds five half-lives (see section 5.2), Lamotrigine PTR Pharma should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that Lamotrigine PTR Pharma not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

Epilepsy

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

Table 1: Adults and adolescents aged 13 years and above – recommended treatment regimen in epilepsy

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy:	25 mg/day (once a day)	50 mg/day (once a day)	100 – 200 mg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved. 500 mg/day has been required by some patients to achieve desired response.
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5)**:**			
This dosage regimen should be used with valproate regardless of any concomitant medicinal products.	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	100 – 200 mg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 25 - 50 mg every one to two weeks until optimal response is achieved.
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine			

glucuronidation (see section 4.5)**:**			
This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	50 mg/day (once a day)	100 mg/day (two divided doses)	200 – 400 mg/day (two divided doses) To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved. 700 mg/day has been required by some patients to achieve desired response.
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5)**:**			
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.	25 mg/day (once a day)	50 mg/day (once a day)	100 – 200 mg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved.
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

Table 2: Children and adolescents aged 2 to 12 years - recommended treatmentregimen in epilepsy (total daily dose in mg/kg body weight/day)

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy of typical absence seizures:	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1 – 10 mg/kg/day (once a day

			or two divided doses), although some patients required higher doses (up to 15 mg/kg/day) to achieve treatment response. To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved with a maximum maintenance dose of 200 mg/day.
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5)**:**			
This dosage regimen should be used with valproate regardless of any other concomitant medicinal products	0.15 mg/kg/day* (once a day)	0.3 mg/kg/day (once a day)	1 – 5 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.3 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day.
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5)**:**			

This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	0.6 mg/kg/day (two divided doses)	1.2 mg/kg/day (two divided doses)	5 – 15 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day.
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5)**:**			
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1 – 10 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum of maintenance dose of 200 mg/day.
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

* If the calculated daily dose in patients taking valproate is 1.5 mg or more but less than 2.5 mg, then a Lamotrigine PTR Pharma 5 mg halved tablet may be taken on alternate days for the first two weeks. If the calculated daily dose in patients

taking valproate is 1 mg or more but less than 1.5 mg, other lamotrigine products containing less active substance may be available for those patients. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. It is likely that patients aged two to six years will require a maintenance dose at the higher end of the recommended range.

If epileptic control is achieved with adjunctive treatment, concomitant AEDs may be withdrawn and patients continued on Lamotrigine PTR Pharma monotherapy.

Abrupt withdrawal of Lamotrigine PTR Pharma may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine PTR Pharma should be gradually decreased over a period of two weeks.

Children below 2 years
There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus Lamotrigine PTR Pharma is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4, 5.1 and 5.2.

Bipolar disorder

The recommended dose escalation and maintenance doses for adults of 18 years of age and above are given in the tables below. The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over six weeks (Table 3) after which other psychotropic medicinal products and/or AEDs can be withdrawn, if clinically indicated (Table 4). The dose adjustments following addition of other psychotropic medicinal products and/or AEDs are also provided below (Table 5). Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

Table 3: Adults aged 18 years and above - recommended dose escalation to the maintenance total daily stabilisation dose in treatment of bipolar disorder

Treatment Regimen	Weeks 1 + 2	Weeks 3 + 4	Week 5	Target Stabilisation Dose (Week 6)*
Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5)**:**				
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day (once a day or two divided doses)	200 mg/day - usual target dose for optimal response (once a day or two divided doses)
				Doses in the range 100 - 400 mg/day used in clinical trials.
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5)**:**				
This dosage regimen should be used with valproate regardless of any concomitant medicinal products.	12.5 mg/day (given as 25 mg on	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day - usual target dose for optimal response

	alternate days)			(once a day or two divided doses)
				Maximum dose of 200 mg/day can be used depending on clinical response.
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5)**:**				
This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	50 mg/day (once a day)	100 mg/day (two divided doses)	200 mg/day (two divided doses)	300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.				

* The target stabilisation dose will alter depending on clinical response

Table 4: Adults aged 18 years and above - maintenance stabilisation total daily dose following withdrawal of concomitant medicinal products in treatment of bipolardisorder

Once the target daily maintenance stabilisation dose has been achieved, other medicinal products may be withdrawn as shown below.

Treatment Regimen	Current lamotrigine stabilisation dose (prior to withdrawal)	Week 1 (beginning with withdrawal)	Week 2	Week 3 onwards *
Withdrawal of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine**:**				
When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week	100 mg/day	200 mg/day	Maintain this dose (200 mg/day) (two divided doses)	
	200 mg/day	300 mg/day	400 mg/day	Maintain this dose (400 mg/day)

Withdrawal of inducers of lamotrigine glucuronidation (see section 4.5), depending on original dose of lamotrigine**:**				
This dosage regimen should be used when the following are withdrawn: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	400 mg/day	400 mg/day	300 mg/day	200 mg/day
	300 mg/day	300 mg/day	225 mg/day	150 mg/day
	200 mg/day	200 mg/day	150 mg/day	100 mg/day
Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)**:**				
This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are withdrawn.	Maintain target dose achieved in dose escalation (200 mg/day; two divided doses) (dose range 100 - 400 mg/day)			
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.				

* Dose may be increased to 400 mg/day as needed

Table 5: Adults aged 18 years and above - adjustment of lamotrigine daily dosing following the addition of other medicinal products in treatment of bipolar disorder

There is no clinical experience in adjusting the lamotrigine daily dose following the addition of other medicinal products. However, based on interaction studies with other medicinal products, the following recommendations can be made:

Treatment Regimen	Current lamotrigine stabilisation dose (prior to addition)	Week 1 (beginning with addition)	Week 2	Week 3 onwards
Addition of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine**:**				
This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products	200 mg/day	100 mg/day	Maintain this dose (100 mg/day)	
	300 mg/day	150 mg/day	Maintain this dose (150 mg/day)	
	400 mg/day	200 mg/day	Maintain this dose (200 mg/day)	
Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate (see section 4.5), depending on original dose of lamotrigine**:**				
This dosage regimen should be used when the following	200 mg/day	200	300 mg/day	400 mg/day

are added without valproate: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir		mg/day		
	150 mg/day	150 mg/day	225 mg/day	300 mg/day
	100 mg/day	100 mg/day	150 mg/day	200 mg/day
Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)**:**				
This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added.	Maintain target dose achieved in dose escalation (200 mg/day; dose range 100-400 mg/day)			
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.				

Discontinuation of Lamotrigine PTR Pharma in patients with bipolar disorder
In clinical trials, there was no increase in the incidence, severity or type of adverse reactions following abrupt termination of lamotrigine versus placebo. Therefore, patients may terminate Lamotrigine PTR Pharma without a step-wise reduction of dose.

Children and adolescents below 18 years
Lamotrigine PTR Pharma is not recommended for use in children below 18 years of age because a randomised withdrawal study demonstrated no significant efficacy and showed increased reporting of suicidality (see section 4.4 and 5.1).

General dosing recommendations for Lamotrigine PTR Pharma in special patient populations

Women taking hormonal contraceptives
The concomitant use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately 2-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as 2-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a 2-fold increase in lamotrigine levels has been observed.
Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation
The maintenance dose of lamotrigine will in most cases need to be increased by as much as 2-fold (see sections 4.4 and 4.5). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 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.
Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine

level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation
The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of lamotrigine 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. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Samples for assessment of lamotrigine levels after permanently stopping the contraceptive pill should not be collected during the first week after stopping the pill.

Starting lamotrigine in patients already taking hormonal contraceptives
Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation
Adjustment to the recommended maintenance dose of lamotrigine may not be required.

Use with other oestrogen-containing products
Other oestrogen-containing therapies, such as hormone replacement therapies (HRTs), may interfere with lamotrigine. Therefore, close clinical monitoring of effectiveness of lamotrigine, including measurements of lamotrigine concentrations may be performed to inform potential dose adjustment as considered appropriate (see section 4.4).

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).

Use with lopinavir/ritonavir
No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing lopinavir/ritonavir therapy. In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

Elderly (above 65 years)
No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population (see section 5.2).

Renal impairment
Caution should be exercised when administering Lamotrigine PTR Pharma to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.4 and 5.2).

Hepatic impairment
Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (see section 5.2).

Method of administration
For oral use.

The tablets should be taken with a glass of water without chewing.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life-threatening rashes such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome (HSS) (see section 4.8).

In adults enrolled in studies utilizing the current lamotrigine 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 Stevens–Johnson syndrome (1 in 1 000). In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1 000.

The risk of serious skin rashes in children is higher than in adults. Available data from a number of studies suggest the incidence of rashes associated with hospitalisation in children is from 1 in 300 to 1 in 100.

In children, the initial presentation of a rash can be mistaken for an infection, physicians should consider the possibility of a reaction to lamotrigine treatment in children that develop symptoms of rash and fever during the first eight weeks of therapy.

Additionally the overall risk of rash appears to be strongly associated with:

- high initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- concomitant use of valproate (see section 4.2).

Caution is also required when treating patients with a history of allergy or rash to other AEDs 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.

All patients (adults and children) who develop a rash should be promptly evaluated and Lamotrigine PTR Pharma withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that Lamotrigine PTR Pharma not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk. If the patient has developed Stevens-Johnson- Syndrome (SJS), Toxic-Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with the use of lamotrigine, treatment with lamotrigine must not be re-started in this patient at any time.

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver, kidney and aseptic meningitis (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example 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 Lamotrigine PTR Pharma discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the active substance in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine

should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

There have also been reports of photosensitivity reactions associated with lamotrigine use (see section 4.8). In several cases, the reaction occurred with a high dose (400 mg or more), upon dose escalation or rapid up-titration. If lamotrigine-associated photosensitivity is suspected in a patient showing signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered.
If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

Haemophagocytic lymphohistiocytosis (HLH)

HLH has been reported in patients taking lamotrigine (see section 4.8). HLH is characterised by signs and symptoms, like 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, HLH can be life threatening.

Patients should be informed of the symptoms associated with HLH and should be advised to seek medical attention immediately if they experience these symptoms while on lamotrigine therapy.

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

Clinical worsening and suicide risk

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications.

A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.

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

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medicinal products for bipolar disorder, including Lamotrigine PTR Pharma. Therefore patients receiving Lamotrigine PTR Pharma 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.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, 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.

Effects of oestrogen-containing products including hormonal contraceptives on lamotrigine efficacy

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately 2-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as 2-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the

week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a treatment-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

The interaction between other oral contraceptive or other oestrogen-containing therapies (such as HRT) and lamotrigine have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy (see section 4.6). However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Renal failure

In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.

Patients taking other medicinal products containing lamotrigine

Lamotrigine PTR Pharma should not be administered to patients currently being treated with any other medicinal products containing lamotrigine without consulting a doctor.

Brugada-type ECG and other cardiac rhythm and conduction abnormalities
Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern has been reported in patients treated with lamotrigine. Based on in vitro findings, lamotrigine could potentially slow ventricular conduction (widening of QRS complex) and induce proarrhythmia at therapeutically relevant concentrations in patients with heart disease. Lamotrigine behaves like a weak class IB antiarrhythmic agent with associated potential risks for serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risks (see section 5.3). At therapeutic doses up to 400 mg/day, lamotrigine did not slow ventricular conduction (widen QRS) or cause QT prolongation in healthy individuals in a thorough QT study. The use of lamotrigine should be carefully considered in patients with clinically important structural or functional heart disease such as Brugada syndrome or other cardiac channelopathies, heart failure, ischemic heart disease, heart block or ventricular arrhythmias. If lamotrigine is clinically justified in these patients, consultation with a cardiologist before initiating lamotrigine should be considered.

Development in children

There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.

Precautions relating to epilepsy

As with other AEDs, abrupt withdrawal of Lamotrigine PTR Pharma may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine PTR Pharma should be gradually decreased over a period of two weeks.

There are reports in the literature that severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation, sometimes with fatal outcome. Similar cases have occurred in association with the use of lamotrigine.

A clinically significant worsening of seizure frequency instead of an 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.

Myoclonic seizures may be worsened by lamotrigine.

There is a suggestion in the data that responses in combination with enzyme inducers is less than in combination with non-enzyme inducing antiepileptic agents. The reason is unclear.

In children taking lamotrigine for the treatment of typical absence seizures, efficacy may not be maintained in all patients.

Precautions relating to bipolar disorder

Children and adolescents below 18 years
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.

Excipients
Lamotrigine PTR Pharma contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Lamotrigine PTR Pharma contains sodium, but less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Medicinal products 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 medicinal products that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in Table 6. Specific dosing guidance for these medicinal products is provided in section 4.2. In addition, this table lists those medicinal products which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such medicinal products 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.

Table 6: Effects of medicinal products on the concentration of lamotrigine

Medicinal products that increase the concentration of lamotrigine	**Medicinal products that decrease the concentration of lamotrigine**	**Medicinal products that have little or no effect on the concentration of lamotrigine**
Valproate	Atazanavir/ritonavir*	Aripiprazole
	Carbamazepine	Bupropion
	Ethinyloestradiol/ levonorgestrel combination*	Felbamate
	Lopinavir/ritonavir	Gabapentin
	Phenobarbitone	Lacosamide
	Phenytoin	Levetiracetam
	Primidone	Lithium

	Rifampicin	Olanzapine
		Oxcarbazepine
		Paracetamol
		Perampanel
		Pregabalin
		Topiramate
		Zonisamide

*For dosing guidance (see section 4.2) plus for women taking hormonal contraceptives also see section 4.4.

Interactions involving antiepileptic drugs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly 2-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

There are reports in the literature of decreased lamotrigine levels when lamotrigine was given in combination with oxcarbazepine. However, in a prospective 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. Therefore, in patients receiving concomitant therapy with oxcarbazepine, the treatment regimen for lamotrigine adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation should be used (see section 4.2).

In a study of healthy volunteers, coadministration of felbamate (1 200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Based on a retrospective analysis of plasma levels in patients who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both active substances during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

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

Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

In a study of patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (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 changes in the plasma concentrations of other AEDs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant AEDs. Evidence from *in vitro* studies indicates that lamotrigine does not displace other AEDs from protein binding sites.

Interactions involving other psychoactive medicinal products

The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day lamotrigine.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

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. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

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 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.

In vitro experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally inhibited by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol or lorazepam. These experiments also suggested that metabolism of lamotrigine was unlikely to be inhibited by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. In addition, a study of bufuralol metabolism using human liver microsome preparations suggested that lamotrigine would not reduce the clearance of medicinal products metabolised predominantly by CYP2D6.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics
In a study of 16 female volunteers, dosing with 30 µg ethinyloestradiol/150 µg levonorgestrel in a combined oral contraceptive pill caused an approximately 2-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately 2-fold higher than during co-therapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics
In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a 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 Cmax, 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.

Interactions involving other medicinal products

In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the appropriate treatment regimen should be used (see section 4.2).

In a study in healthy volunteers, lopinavir/ritonavir approximately halved the plasma concentrations of lamotrigine, probably by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

In a study in healthy adult volunteers, paracetamol 1 g (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 demonstrate that lamotrigine, but not the N(2)- glucuronide metabolite, is an inhibitor of Organic Transporter 2 (OCT 2) at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with an IC_{50} value of 53.8 µM. Co-administration of lamotrigine with renally excreted medicinal products, which are substrates of OCT 2 (e.g. metformin, gabapentin and varenicline), may result in increased plasma levels of these medicinal products.
The clinical significance of this has not been clearly defined, however care should be taken in patients co-administered with these medicinal products.

4.6 Fertility, pregnancy and lactation

Risk related to antiepileptic drugs in general

Specialist advice should be given to women who are of childbearing potential. The antiepileptic treatment should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Risk related to lamotrigine

Pregnancy
A large amount of data on pregnant women exposed to lamotrigine monotherapy during the first trimester of pregnancy (more than 8 700) 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 Lamotrigine PTR Pharma 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.

Lactation
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 breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant. Should a woman decide to breast-feed while on therapy with lamotrigine, the infant should be monitored for adverse effects, such as sedation, rash and poor weight gain.

Fertility
Animal experiments did not reveal impairment of fertility by lamotrigine (see section 5.3).

4.7 Effects on ability to drive and use machines

As there is individual variation in response to all AED therapy, patients taking Lamotrigine PTR Pharma to treat epilepsy should consult their physician on the specific issues of driving and epilepsy.

No studies on the effects on the ability to drive and use machines have been performed. Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how Lamotrigine PTR Pharma therapy affects them before driving or operating machinery.

4.8 Undesirable effects

The undesirable effects for epilepsy and bipolar disorder indications are based on available data from controlled clinical studies and other clinical experience and are listed in the table below. Frequency categories are derived from controlled clinical studies (epilepsy monotherapy (identified by†) and bipolar disorder (identified by §)). Where frequency categories differ between clinical trial data from epilepsy and bipolar disorder the most conservative frequency is shown. However, where no controlled clinical trial data are available, frequency categories have been obtained from other clinical experience.

The following convention has been utilised for the classification of undesirable effects:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).

System Organ Class	Adverse Event	Frequency
Blood and lymphatic system disorders	Haematological abnormalities[1] including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis Haemophagocytic lymphohistiocytosis (see section 4.4)	Very rare
	Lymphadenopathy[1], pseudolymphoma	Not known
Immune System Disorders	Hypersensitivity syndrome[2]	Very rare
	Hypogammaglobulinaemia	Not known
Psychiatric Disorders	Aggression, irritability	Common
	Confusion, hallucinations, tics (motor and/or phonic tics)	Very rare
	Acute psychotic reactions (e.g. paranoia, mania, delusions), nightmares, obsessive-compulsive disorder	Not known
Nervous System Disorders	Headache†§	Very common
	Somnolence†§, dizziness†§, tremor†, insomnia†, agitation§	Common
	Ataxia†	Uncommon
	Nystagmus†, aseptic meningitis (see section 4.4)	Rare
	Unsteadiness, movement disorders, worsening of Parkinson's disease [3], extrapyramidal effects, choreoathetosis†, increase in seizure frequency	Very rare
Eye disorders	Diplopia†, blurred vision†	Uncommon
	Conjunctivitis	Rare
Gastrointestinal disorders	Nausea†, vomiting†, diarrhoea†, dry mouth§	Common
Hepatobiliary disorders	Hepatic failure, hepatic dysfunction[4], increased liver function tests	Very rare
Skin and subcutaneous tissue disorders	Skin rash[5]†§	Very common
	Alopecia, photosensitivity reaction	Uncommon
	Erythema multiforme, Stevens–Johnson Syndrome§ (see section 4.4)	Rare
	Toxic epidermal necrolysis (see section 4.4), Drug Reaction with Eosinophilia and Systemic Symptoms[2] (see section 4.4)	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia§	Common
	Lupus-like reactions	Very rare
Renal and urinary disorders	Tubulointerstitial nephritis, tubulointerstitial nephritis and uveitis syndrome	Not known
General disorders and administration site conditions	Tiredness†, pain§, back pain§	Common

Description of selected adverse reactions

[1] Haematological abnormalities and lymphadenopathy may or may not be associated with the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / hypersensitivity syndrome (see section 4.4 and "Immune system disorders").

[2] Rash has also been reported as part of this syndrome, also known as DRESS. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, and abnormalities of the blood, liver and kidney. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example 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 Lamotrigine PTR Pharma discontinued if an alternative aetiology cannot be established (see section 4.4).

[3] These effects have been reported during other clinical experience.
There have been reports that lamotrigine may worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

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

[5] In clinical trials in adults, skin rashes occurred in up to 8-12% of patients taking lamotrigine and in 5-6% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamotrigine PTR Pharma (see section 4.4).

Serious potentially life-threatening skin rashes, including Stevens–Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Although the majority recover on withdrawal of lamotrigine treatment, 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 lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- concomitant use of valproate (see section 4.2).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms and signs

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has been reported, including fatal cases. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness, worsening of seizures, grand mal convulsion, ECG changes, e.g. broadening of the QRS complex (intraventricular conduction delay) and QT prolongation, tachycardia and coma. Broadening of QRS duration to more than 100 msec may be associated with more severe toxicity.

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

Pharmacotherapeutic group: other antiepileptics,
ATC code: N03AX09.

Mechanism of action

The results of pharmacological studies suggest that lamotrigine is a use- and voltage-dependent blocker of voltage gated sodium channels. It inhibits sustained repetitive firing of neurones and inhibits release of glutamate (the neurotransmitter which plays a key role in the generation of epileptic seizures). These effects are likely to contribute to the anticonvulsant properties of lamotrigine.

In contrast, the mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established, although interaction with voltage gated sodium channels is likely to be important.

Pharmacodynamic effects

In tests designed to evaluate the central nervous system effects of medicinal products, the results obtained using doses of 240 mg lamotrigine administered to healthy volunteers did not differ from placebo, whereas both 1 000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor co-ordination and eye movements, increased body sway and produced subjective sedative effects.

In another study, single oral doses of 600 mg carbamazepine significantly impaired fine visual motor co-ordination and eye movements, while increasing both body sway and heart rate, whereas results with lamotrigine at doses of 150 mg and 300 mg did not differ from placebo.

Study of the effect of lamotrigine on cardiac conduction
A study in healthy adult volunteers evaluated the effect of repeat doses of lamotrigine (up to 400 mg/day) on cardiac conduction, as assessed by 12-lead ECG. There was no clinically significant effect of lamotrigine on QT interval compared to placebo.

Clinical efficacy and safety

Prevention of mood episodes in patients with bipolar disorder
The efficacy of lamotrigine in the prevention of mood episodes in patients with bipolar I disorder has been evaluated in two studies.
Study SCAB2003 was a multicentre, double-blind, double dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using lamotrigine monotherapy or adjunctive therapy, patients were randomly assigned into one of five treatment groups: lamotrigine (50, 200, 400 mg/day), lithium (serum levels of 0.8 to 1.1 mMol/L) or placebo for a maximum of 76 weeks (18 months). The primary endpoint was "Time to Intervention for a Mood Episode (TIME)", where the interventions were additional pharmacotherapy or electroconvulsive therapy (ECT). Study SCAB2006 had a similar design as study SCAB2003, but differed from study SCAB2003 in evaluating a flexible dose of lamotrigine (100 to 400 mg/day) and including patients with bipolar I disorder who had recently or were currently experiencing a manic episode. The results are shown in Table 7.

Table 7: Summary of results from studies investigating the efficacy of lamotrigine in the prevention of mood episodes in patients with bipolar I disorder

'Proportion' of patients being event free at week 76						
	Study SCAB2003			**Study SCAB2006**		

	Bipolar I			**Bipolar I**		
Inclusion criterion	Major depressive episode			Major manic episode		
	Lamotrigine	Lithium	Placebo	Lamotrigine	Lithium	Placebo
Intervention free	0.22	0.21	0.12	0.17	0.24	0.04
p-value Log rank test	0.004	0.006	-	0.023	0.006	-
Depression free	0.51	0.46	0.41	0.82	0.71	0.40
p-value Log rank test	0.047	0.209	-	0.015	0.167	-
Free of mania	0.70	0.86	0.67	0.53	0.64	0.37
p-value Log rank test	0.339	0.026	-	0.280	0.006	-

In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine-treated patients had significantly longer times to first depressive episode than placebo patients, and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

The efficacy of lamotrigine in combination with mood stabilisers has not been adequately studied.

Paediatric population

Children aged 1 to 24 months
The efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets are the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase (for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant: 26.3%, CI 95% -2.6% <> 50.2%, p=0.07.

A total of 256 subjects between 1 to 24 months of age have been exposed to lamotrigine in the dose range 1 to 15 mg/kg/day for up to 72 weeks. The safety profile of lamotrigine in children aged 1 month to 2 years was similar to that in older children except that clinically significant worsening of seizures (>=50%) was reported more often in children under 2 years of age (26%) as compared to older children (14%).

Lennox-Gastaut syndrome
There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

Prevention of mood episodes in children (10 - 12 years of age) and adolescents (13 - 17 years of age)
A multicentre, parallel group, placebo-controlled, double-blind, randomised withdrawal study, evaluated the efficacy and safety of lamotrigine IR as add-on maintenance therapy to delay mood episodes in male and female children and adolescents (age 10-17 years) who had been diagnosed with bipolar I disorder and who had remitted or improved from a bipolar episode while treated with lamotrigine in combinations with concomitant antipsychotic or other mood-stabilising drugs. The result of the primary efficacy analysis (time to occurrence of a bipolar event – TOBE) did not reach statistical significance (p=0.0717), thus efficacy was not shown. In addition, safety results showed increased reporting of suicidal behaviours in lamotrigine treated patients: 5% (4 patients) in the lamotrigine arm compared to 0 in placebo (see section 4.2).

5.2 Pharmacokinetic properties

Absorption

Lamotrigine is rapidly and completely absorbed from the gut with no significant first-pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral administration of lamotrigine. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations rarely vary.

Distribution
Binding to plasma proteins is about 55%; it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 L/kg.

Biotransformation
UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine.
Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P_{450} enzymes are unlikely to occur.

Elimination
The apparent plasma clearance in healthy subjects is approximately 30 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of lamotrigine-related material is excreted in faeces. Clearance and half-life are independent of dose. The apparent plasma half-life in healthy subjects is estimated to be approximately 33 hours (range 14 to 103 hours). In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.
The half-life of lamotrigine is greatly affected by concomitant medicinal products. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing medicinal products such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see section 4.2).

Linearity
The pharmacokinetics of lamotrigine are linear up to 450 mg, the highest single dose tested.

Special patient populations

Children
Clearance adjusted for body weight is higher in children than in adults with the highest values in children under five 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 medicinal products such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with valproate alone (see section 4.2).

Infants aged 2 to 26 months
In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher Cmax levels are likely to be observed in some children with a body weight below 10 kg.

Elderly
Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. 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 nine studies with non-elderly adults after single doses of 30 to 450 mg.

Renal impairment
Twelve volunteers with chronic renal failure, and another six individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances 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 with 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 with 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 the patient's concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

Hepatic impairment
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. 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 with 0.34 mL/min/kg in the healthy controls. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but reduced foetal weight and retarded skeletal ossification were observed, at exposure levels below or similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to the severity of maternal toxicity, the teratogenic potential of lamotrigine has not been characterised above clinical exposure.

In rats, enhanced foetal as well as post-natal mortality was observed when lamotrigine was administered during late gestation and through the early post-natal period. These effects were observed below the expected clinical exposure.

In juvenile rats, an effect on learning in the Biel maze test, a slight delay in balanopreputial separation and vaginal patency and a decreased postnatal body weight gain in F1 animals were observed at exposures less than the therapeutic exposures in human adults, based on body surface area.

Animal experiments did not reveal impairment of fertility by lamotrigine. Lamotrigine reduced foetal folic acid levels in rats. Folic acid deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC_{50} was approximately 9-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately 2-times the maximum therapeutic free concentration. In a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers (see section 5.1).

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 (see section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Povidone
Magnesium stearate
Talc
Silica, colloidal anhydrous
Iron oxide yellow (E-172) (only 100 mg tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinalproduct does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu blisters containing 30, 50, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

PTR Pharma Consulting Lda
Rua Brito Pais 8C
Miraflores
Alges
Lisbon
1495-028
Portugal

8 MARKETING AUTHORISATION NUMBER

PA25273/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th July 2026

10 DATE OF REVISION OF THE TEXT