SUMMARY OF PRODUCT CHARACTERISTICS

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EPSYLAM DT

(Lamotrigine Dispersible Tablets 5 mg, 25 mg, 50 mg, 100 mg and 200 mg)

R_x Only

1. NAME OF THE MEDICINAL PRODUCT: Lamotrigine Dispersible Tablets 5 mg
Lamotrigine Dispersible Tablets 25 mg
Lamotrigine Dispersible Tablets 50 mg
Lamotrigine Dispersible Tablets 100 mg
Lamotrigine Dispersible Tablets 200 mg

(TRADE) NAME OF PRODUCT **:** EPSYLAM DT 5
EPSYLAM DT 25
EPSYLAM DT 50
EPSYLAM DT 100
EPSYLAM DT 200

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lamotrigine Dispersible Tablets 5 mg

Each uncoated tablet contains Lamotrigine Ph.Eur. 5 mg

Lamotrigine Dispersible Tablets 25 mg

Each uncoated tablet contains Lamotrigine Ph.Eur. 25 mg

Lamotrigine Dispersible Tablets 50 mg

Each uncoated tablet contains Lamotrigine Ph.Eur. 50 mg

Lamotrigine Dispersible Tablets 100 mg

Each uncoated tablet contains Lamotrigine Ph.Eur. 100 mg

Lamotrigine Dispersible Tablets 200 mg

Each uncoated tablet contains Lamotrigine Ph.Eur. 200 mg

3. PHARMACEUTICAL FORM

Lamotrigine Dispersible Tablets 5 mg

White to off-white, capsule shaped uncoated tablets debossed with ‘H’ on one side and ‘81’ on other side.

Lamotrigine Dispersible Tablets 25 mg

White to off-white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '80' on flat side.

Lamotrigine Dispersible Tablets 50 mg

White to off-white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '79' on flat side.

Lamotrigine Dispersible Tablets 100 mg

White to off-white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '78' on flat side.

Lamotrigine Dispersible Tablets 200 mg

White to off-white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '77' on flat side.

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. Epsylam DT 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.

Epsylam DT is not indicated for the acute treatment of manic or depressive episodes.

4.2 Posology and method of administration

Epsylam DT tablets should be swallowed whole, and should not be chewed or crushed.

Epsylam DT tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

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

Restarting therapy

Prescribers should assess the need for escalation to maintenance dose when restarting Epsylam DT in patients who have discontinued Epsylam DT for any reason, since the risk of serious rash may be associated with high initial doses and exceeding the recommended dose escalation for lamotrigine. 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, Epsylam DT should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that Epsylam DT 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.

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.

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)			
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 everyone to two weeks until optimal response is achieved
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation			
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			
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 the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

Table 2: Children and adolescents aged 2 to 12 years - recommended treatment regimen 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)	0.6mg/kg/day (once a day or two divided doses)	- 15 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 maintenance dose of 200mg/day
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation)			
This dosage regimen should be used with valproate regardless of any concomitant medicinal products	0.15 mg/kg/day* (once a day)	0.3mg/kg/day (once a day)	- 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			
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)	1.2mg/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			
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 the treatment regimen as recommended for lamotrigine with concurrent			

valproate should be used.
* If the calculated daily dose in patients taking valproate is 1 mg or more but less than 2 mg, then Lamotrigine 2 mg chewable/dispersible tablets may be taken on alternate days for the first two weeks. 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 Lamtrogine monotherapy.

Children below 2 years

Epsylam DT is not recommended for use in children below 2 years of age.

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.

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				
This dosage regimen should beused with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	25mg/day(once a day)	50 mg/day (once a day or two divided doses)	100mg/day (once a day or two divided doses)	200 mg/day - usual target dose for optimal response (once a day or two divided doses)
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation)				
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)	50 mg/day (once a day or two divided doses)	100 mg/day - usual target dose for optimal response (once a day or two divided doses)
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation				
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,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 bipolar disorder

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 addition)**	**Week 1 (beginning with addition)**	**Week 2**	**Week 3 onwards***
Withdrawal of valproate (inhibitor of lamotrigine glucuronidation) 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 ,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				
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,the treatment regimen recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment				

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

Discontinuation of Epsylam DT in patients with bipolar disorder

Patients may terminate Epsylam DT without a step-wise reduction of dose.

Children and adolescents below 18 years

Epsylam DT 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.

General dosing recommendations for Epsylam DT in special patient populations

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, 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 are added without valproate: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	200 mg/day	200 mg/day	300 mg/day	400 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:				
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, the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.				

Discontinuation of Lamotrigine in patients with bipolar disorder

Patients may terminate Lamotrigine without a step-wise reduction of dose.

Children and adolescents below 18 years

Lamotrigine 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.

General dosing recommendations for Lamotrigine in special patient populations

Women taking hormonal contraceptives

The use of an ethinyloestradiol/levonorgestrel (30µg/150µg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-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).

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 two-fold. 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.

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%. 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 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.

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.

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.

Renal impairment

Caution should be exercised when administering Lamotrigine 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.

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.

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 8 weeks after initiation of Lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalization and discontinuation of lamotrigine may be 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).

The risk of serious skin rashes in children is higher than in adults.

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.
- Concomitant use of valproate.

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.

All patients (adults and children) who develop a rash should be promptly evaluated and Epsylam DT withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that Epsylam DT 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 SJS, TEN or 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 a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver and aseptic meningitis. 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 Epsylam DT discontinued if an alternative aetiology cannot be established.

Aseptic meningitis may be reversible on withdrawal of the drug in most cases, but recurred in a number of cases on reexposure 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.

<u>Haemophagocytic lymphohistiocytosis (HLH)</u>

HLH has been reported in patients taking lamotrigine. 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 medications for bipolar disorder, including Lamotrigine. Therefore patients receiving Lamotrigine 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.

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately two-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 two-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. Variations in lamotrigine levels of this order may be associated with adverse effects. 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).

The interaction between other oral contraceptive or HRT treatments 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. 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 preparations containing lamotrigine

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

Brugada-type ECG

Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern has been reported in patients treated with lamotrigine. The use of lamotrigine should be carefully considered in patients with Brugada syndrome.

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 may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine 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.

4.5 Interaction with other medicinal products and other forms of interaction

Uridine 5-diphospho (UDP) glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs 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.

Those drugs that have been demonstrated to have a clinically significant impact on lamotrigine metabolism are outlined in Table 6.

Table 6: Effects of other medicinal products on glucuronidation of lamotrigine

Medicinal products that significantly inhibit glucuronidation of lamotrigine	**Medicinal products that significantly induce glucuronidation of lamotrigine**	**Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine**
Valproate	Phenytoin	Oxcarbazepine
	Carbamazepine	Felbamate
	Phenobarbitone	Gabapentin
	Primidone	Levetiracetam
	Rifampicin	Pregabalin
	Lopinavir/ritonavir	Topiramate
	Ethinyloestradiol/ levonorgestrel combination**	Zonisamide
	Atazanavir/ritonavir*	Lithium
		Buproprion
		Olanzapine
		Aripiprazole
		Lacosamide
		Perampanel

*For dosing guidance (see section 4.2)

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.

**Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see section 4.2 and 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 two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used.

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, pheonbarbitone or primidone, the appropriate treatment regimen should be used.

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 1200 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.

In a study of healthy volunteers, coadministration of felbamate (1200 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 agents 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%. An effect of this magnitude is not considered to be clinically relevant.

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.

<u>Interactions involving other psychoactive agents</u>

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 Cmax of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. 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 Cmax and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

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 two-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 two-fold higher than during co-therapy. 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.

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. 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.

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.

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.

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 IC50 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 Pregnancy

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 might have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs may 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 8700) do not suggest a substantial increase in the risk for major congenital malformations, including oral clefts.

If therapy with Epsylam DT 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 mother's. 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.

4.7 Effects on ability to drive and use machines

As there is individual variation in response to all antiepileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: Very common (≥1/10); common(≥1/100 to <1/10); uncommon (≥1/1000 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	Very rare
	Haemophagocytic lymphohistiocytosis	Very rare
	Lymphadenopathy[1]	Not known
Immune System Disorders	Hypersensitivity syndrome[2] (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi organ failure).	Very Rare
	Hypogammaglobulinaemia	Unknown
Psychiatric Disorders	Aggression, irritability	Common
	Confusion, hallucinations, tics	Very rare
	Nightmares	Not known
Nervous System Disorders	Headache	Very Common
	Somnolence, dizziness, tremor, insomnia, agitation	Common
	Ataxia	Uncommon
	Nystagmus	Rare
	Unsteadiness, movement disorders, worsening of Parkinson's disease[3], extrapyramidal effects, choreoathetosis, increase in seizure frequency	Very Rare
	Aseptic meningitis	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	Very rare
Skin and subcutaneous tissue disorders	Skin rash[5]	Very common
	Alopecia	Uncommon
	Stevens–Johnson Syndrome	Rare
	Toxic epidermal necrolysis	Very rare
	Drug Reaction with Eosinophilia and Systemic Symptoms	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Lupus-like reactions	Very rare
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 hypersensitivity syndrome.

2 Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and

abnormalities of the blood and liver. 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 discontinued if an alternative aetiology cannot be established.

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.

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.

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.
- concomitant use of valproate.

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms.

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

4.9 Overdose

Symptoms and signs

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose may be reported,including fatal cases. Overdose may result in symptoms including nystagmus, ataxia, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) may be observed in overdose patients. Broadening of QRS duration to more than 100 msec may be associated with more severe toxicity.

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.

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 drug administration. 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 P450 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.

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.

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 coadministered 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 hemodialysis 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 hemodialysis) and 1.57 mL/min/kg (during hemodialysis), 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 hemodialysis) and 13.0 hours (during hemodialysis), 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 hemodialysis 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose Microcrystalline (PH 101), Magnesium Carbonate, Heavy, Polacrilin Potassium, Sucralose, Povidone, Purified Water, Cellulose Microcrystalline (PH 102), Black Currant Flavour 501017 AP 0551 and Magnesium Stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer outer package for expiry date.

6.4 Special precautions for storage

Store in a dry place below 30°C.

6.5 Nature and contents of container

Blister pack

Lamotrigine Dispersible Tablets 5 mg – 3 x 10’s Tablets

Lamotrigine Dispersible Tablets 25 mg – 3 x 10’s Tablets

Lamotrigine Dispersible Tablets 50 mg – 3 x 10’s Tablets

Lamotrigine Dispersible Tablets 100 mg – 3x 10’s Tablets

Lamotrigine Dispersible Tablets 200 mg – 3x 10’s Tablets

6.6 Manufactured By:

Aurobindo Pharma Ltd., Unit-III,

Survey No. 313 & 314, Bachupally, Bachupally Mandal,

Medchal-Malkajgiri District,

Telangana State, India.

6.7 Marketing Authorisation Holder

AUROBINDO

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7. DATE OF PREPARATION OF THIS LEAFLET

May 2020.