יוני 2020

הנדון: למיקטל טבליות מסיסות/לעיסות 2,5,25,50,100,200 מ"ג
Lamictal Dispersible/Chewable Tablets 2,5,25,50,100,200mg

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלונים לרופא ולצרכן של כלל מינוני : **Lamictal Dispersible/Chewable tablets.**

העדכונים בעלונים כללו <u>עדכון בסעיפים התוויה ומינונים</u> של התכשיר ושינויים רבים אחרים. <u>על כן יש לקרוא את העלונים בעיון מתחילתם ועד סופם.</u>

בהודעה זו כלולים השינויים מהותיים בלבד בעלונים לרופא ולצרכן. בעלונים ישנם שינויים נוספים.

מרכיבים פעילים וחוזקם:

Lamictal Dispersible/Chewable Tablets 2: Lamotrigine – 2 mg
Lamictal Dispersible/Chewable Tablets 5: Lamotrigine – 5 mg
Lamictal Dispersible/Chewable Tablets 25: Lamotrigine – 25 mg
Lamictal Dispersible/Chewable Tablets 50: Lamotrigine – 50 mg
Lamictal Dispersible/Chewable Tablets 100: Lamotrigine – 100 mg
Lamictal Dispersible/Chewable Tablets 200: Lamotrigine – 200 mg

ההתוויה שאושרה ע"י משרד הבריאות:

Epilepsy (Lamictal Disp/Chewable Tablets : 2MG, 5MG, 25MG, 50MG, 100MG, 200MG)

- 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. Lamictal 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 (Lamictal Disp/Chewable Tablets : 25MG, 50MG, 100MG, 200MG)

- 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).

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

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא :

4.1 Therapeutic indications

~~Epilepsy~~

- ~~*Monotherapy in adults and children over 12 years of age:*~~

~~Simple partial seizures.~~
~~Complex partial seizures.~~
~~Secondarily generalised tonic clonic seizures.~~
~~Primary generalised tonic clonic seizures.~~
~~Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.~~

~~Add-on therapy in adults and children over 2 years of age:~~
~~Simple partial seizures.~~
~~Complex partial seizures.~~
~~Secondarily generalised tonic clonic seizures.~~

~~BIPOLAR DISORDER~~
~~(Lamictal Disp/Chewable Tablets: 25MG, 50MG, 100MG, 200MG)~~

- ~~Adults (18 years of age and over)~~

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

Epilepsy
(Lamictal Disp/Chewable Tablets : 2MG, 5MG, 25MG, 50MG, 100MG, 200MG)

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. Lamictal 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
(Lamictal Disp/Chewable Tablets : 25MG, 50MG, 100MG, 200MG)

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).

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

4.2 Posology and method of administration

Lamictal chewable/dispersible 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 Lamictal in patients who have discontinued Lamictal 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), Lamictal should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that Lamictal 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 ~~or induce lamotrigine glucuronidation (see Interactions)~~ 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 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)	0.6 mg/kg/day (once a day or two divided doses)	1 – 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 – 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 ~~Or with other inducers of lamotrigine glucoronidation (see Interactions)~~ 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 mg or more but less than 2 mg, then Lamictal 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 Lamictal should not be administered.			

~~**Table 4**~~

~~Weight based dosing can be achieved by using the following guide:~~			
~~If the patient's weight is~~		~~Give this daily dose, using the most appropriate combination of Lamictal 2 r and 5 mg tablets~~	
~~Greater than~~	~~And less than~~	~~Weeks 1 and 2~~	~~Weeks 3 and 4~~
~~6.7 kg~~	~~14 kg~~	~~2 mg every other day~~	~~2 mg every day~~
~~14.1 kg~~	~~27 kg~~	~~2 mg every day~~	~~4 mg every day~~

27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amo to the previously administered daily dose			

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 Lamictal monotherapy

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 Lamictal 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).

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

Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with lamotrigine in mania has not been conclusively established

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 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) 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 ~~Or with other inducers of lamotrigine glucuronidation (see Interactions)~~ 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, shou be used.				

* The Target stabilisation dose will alter depending on clinical response

~~**Adjunct therapy with inhibitors of lamotrigine glucoronidation e.g. Valproate.** In patients taking glucoronidation (a inhibiting concomitant drugs such as valproate the initial lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. The dose should be increased to 50 mg once a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 100 mg/day given once a day or in two divided doses. However, the dose can be increased to a maximum daily dose of 200 mg, depending on clinical response.~~

~~**Adjunct therapy with inducers of lamotrigine glucoronidation in patients NOT taking inhibitors such as (b Valproate This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other drugs known to induce lamotrigine glucuronidation** (see Interactions). In those patients currently taking drugs that induce lamotrigine glucoronidation and NOT taking valproate, the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. The dose should be increased to 200 mg/day given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day however, the usual target dose to achieve optimal response is 400 mg/day given in two divided doses which may be given from week 7.~~

~~Monotherapy with lamotrigine OR adjunctive therapy in patients taking other medications that do not significantly (c induce or inhibit lamotrigine glucuronidation (see Interactions). The initial lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100 to 400 mg was used in clinical trials.~~

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 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 ~~Or with other inducers of lamotrigine glucuronidation (see Interactions)~~ 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

~~**Following withdrawal of adjunct therapy with inhibitors of lamotrigine glucoronidation e.g. valproate.** The (a) dose of lamotrigine should be increased to double the original target stabilisation dose and maintained at this, once valproate has been terminated.~~

~~**Following withdrawal of adjunct therapy with inducers of lamotrigine glucoronidation depending on original maintenance dose.** (b) This regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone or other drugs known to induce lamotrigine glucuronidation (see Interactions). The dose of lamotrigine should be gradually reduced over three weeks as the enzyme inducer is withdrawn.~~

~~**Following withdrawal of adjunct therapy with other** medications that do not significantly inhibit or induce (c) lamotrigine glucuronidation (see Interactions). The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.~~
~~**Adjustment of lamotrigine daily dosing in patients with BIPOLAR DISORDER following addition of other medications:** There is no clinical experience in adjusting the lamotrigine daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made (see Table 7, below)~~

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 are added without valproate: phenytoin carbamazepine phenobarbitone ~~Or with other inducer of lamotrigine glucuronidation (see Interactions)~~ 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 (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 Lamictal 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 Lamictal without a step-wise reduction of dose.

Children and adolescents below 18 years
Lamictal is not recommended for use in children below 18 years of age ~~Safety and efficacy of lamotrigine in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.~~ 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 Lamictal in special patient populations

Women taking hormonal contraceptives
~~Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see Warnings and Precautions and Interactions), no adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether lamotrigine is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation,or whether lamotrigine is added in the absence of valproate or an inducer of lamotrigine glucuronidation (see Table 2 for epilepsy and Table 5 for bipolar disorder patients).~~
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. 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; 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 two-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 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 Lamictal 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).

4.4 Special warnings and precautions for use

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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.

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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.

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Precautions relating to epilepsy

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

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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. 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. Specific dosing guidance for these drugs is provided in Section 4.2.

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

**Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see sections 4.2 and 4.4).

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.

…

4.8 Undesirable effects

…

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) Lymphadenopathy[1]	Very rare Very rare 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). Hypogammaglobulinaemia	Very Rare Unknown

…

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לצרכן :

1. <u>למה מיועדת התרופה?</u>

~~מבוגרים, מתבגרים וילדים מעל גיל 12 שנה:~~
~~כטיפול יחיד באפילפסיה בלמיקטל , פרכוסים חד-צדדיים ופרכוסים כלליים טונים-קלוניים.~~

~~מבוגרים, מתבגרים וילדים מעל גיל שנתיים :~~
~~כטיפול משולב באפילפסיה, פרכוסים חד-צדדיים ופרכוסים כלליים טונים-קלוניים במקרים שאינם נשלטים על ידי תרופות אחרות.~~

~~מבוגרים (מגיל 18 ומעלה):~~
~~למיקטל טבליות מסיסות/לעיסות 25 מ"ג, 50 מ"ג , 100 מ"ג , 200 מ"ג - למניעת הפרעות במצבי הרוח בעיקר מצבי דיכאון אצל חולים עם הפרעה דו-קוטבית (Bipolar disorder).~~

למיקטל מיועדת לטיפול באפילפסיה (למיקטל טבליות מסיסות/לעיסות: 2,5,25,50,100,200 מ"ג)
במבוגרים ומתבגרים מגיל 13 שנים ומעלה:
- למיקטל ניתנת כטיפול יחיד או משולב עם תרופות אחרות לטיפול בפרכוסים חד צדדיים ופרכוסים כלליים, כולל פרכוסים טונים קלוניים.
- פרכוסים המופיעים במצב של סינדרום לנוקס- גסטאוט (Lenox-Gastaut syndrome). למיקטל ניתנת כטיפול משולב יחד עם תרופות אחרות אבל יכולה לשמש גם כתרופה אנטי-אפילפטית ראשונה, איתה יתחיל הטיפול בסינדרום לנוקס-גסטאוט.

בילדים ומתבגרים בין הגילאים 2 עד 12 שנים :
- למיטקל ניתנת כטיפול משולב עם תרופות אחרות לטיפול בפרכוסים חד צדדיים ופרכוסים כלליים, כולל פרכוסים טונים קלוניים ופרכוסים המופיעים במצב של סינדרום לנוקס-גסטאוט
- למיקטל ניתנת כטיפול יחיד בהתקפי ניתוק טיפוסיים (typical absence seizures)

למיקטל מיועדת לטיפול בהפרעה דו-קטבית (Bipolar disorder) (למיקטל טבליות מסיסות/לעיסות: 25,50,100,200 מ"ג)
במבוגרים מגיל 18 שנים ומעלה:
- למיקטל ניתנת למניעת תקופות הדכאון במטופלים הסובלים מהפרעה דו-קוטבית I אשר חווים בעיקר תקופות דכאון.

למיקטל אינה מיועדת לטיפול מיידי (אקוטי) בתקופות דיכאון או מאניה.

קבוצה תרפויטית
למיקטל שייכת לקבוצת תרופות הנקראת תרופות *נוגדות פרכוסים*.

למיקטל חוסמת אותות במוח אשר מעוררים התקפים אפילפטיים.

2. לפני שימוש בתרופה

…

אזהרות מיוחדות הנוגעות לשימוש בתרופה

…

אם אתה סובל ממצב המכונה תסמונת ברוגדה (Brugada syndrome). תסמונת ברוגדה הינה מחלה גנטית הגורמת לפעילות חשמלית לא תקינה בלב. למיקטל עלולה לגרום לחריגות ב- א.ק.ג אשר עלולות להוביל לאריתמיה (קצב לב לא תקין)

…

מידע חשוב על תגובות שעלולות לסכן להיות מסכנות חיים

…

המופאגוציטיק לימפוהיסטיוציטוזיס (**Haemophagocytic lymphohistiocytosis (HLH)**)
ישנם דיווחים על תגובה נדירה אבל מאוד חמורה של מערכת החיסון במטופלים הנוטלים למיקטל.
צור קשר עם הרופא שלך או עם הרוקח באופן מיידי, אם אתה חווה את אחד מהתסמינים הבאים בזמן נטילת למיקטל: חום, פריחה, תסמינים במערכת העצבים (כגון: רעידות, בלבול, הפרעות בתפקוד המוחי)

…

הריון והנקה

…

אם את מניקה או מתכננת להניק, פני לרופא או לרוקח שלך לקבלת יעוץ לפני נטילת תרופה זו. המרכיב הפעיל של למיקטל עובר לחלב האם ועלול להשפיע על התינוק שלך. הרופא שלך ידון איתך בסיכונים וביתרונות שבהנקה בזמן שאת נוטלת למיקטל ויבדוק את התינוק שלך מפעם לפעם. אם מופיעים אצלו נמנום, פריחה או עלייה מועטה במשקל, ~~את~~ במידה ותחליטי להניק.
יידעי את הרופא שלך אם את מבחינה באחד מהתסמינים הללו אצל תינוקך.

4. תופעות לוואי

…

תגובות שעלולות לסכן חיים: פנה מיד לקבלת סיוע רפואי

…

המופאגוציטיק לימפוהיסטיוציטוזיס (Haemophagocytic lymphohistiocytosis (HLH)) (ראה סעיף 2: אזהרות מיוחדות הנוגעות לשימוש בתרופה)

…

תופעות לוואי נדירות מאוד
תופעות שעלולות להופיע ב- **עד 1 מכל 10,000** משתמשים:

…

- המופאגוציטיק לימפוהיסטיוציטוזיס (Haemophagocytic lymphohistiocytosis (HLH)) (ראה סעיף 2: אזהרות מיוחדות הנוגעות לשימוש בתרופה)

תופעות לוואי אחרות
תופעות לוואי אחרות התרחשו במספר קטן של משתמשים אך שכיחותן המדויקת אינה ידועה:

…

- ירידה ביעילות מערכת החיסון, עקב רמות נמוכות של נוגדנים בשם אימונוגלובולינים בדם אשר מסייעים בהגנה מפני זיהומים.

מקרא לעדכונים המסומנים :
מידע שהוסר – מסומן בקו אדום חוצה ~~XXX~~
תוספת – כתב **כחול**
תוספת החמרה - כתב **כחול** – מסומן בצהוב מרקר

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
טניה רשקובן
רוקחת ממונה