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藥物不良反應工作小組藥物安全警訊通告 107.05

美國食品藥物管理署(FDA)用藥安全資訊風險溝通：

Lamotrigine可能引起嚴重噬血細胞淋巴組織增生症(HLH)的風險

摘要說明:

Lamotrigine 自 1994 年於美國核准後已上市 24 年，主要用於治療兩歲以上癲癇病人或雙極性情感障礙。包括其學名藥在內，統計通報至美國食品藥物管理署(FDA)之藥物不良反應，已經確定有 8 名大人或小孩確定及疑似因服用 Lamotrigine 導致噬血細胞淋巴組織增生症 hemophagocytic lymphohistiocytosis (HLH)，此為罕見但嚴重的免疫過度激活反應。HLH 症狀有持續性發燒(通常>38 ℃)，產生血液學及器官(肝、腎、肺及脾等)的嚴重問題，甚至導致住院及死亡。

Lamictal ® (Lamotrigine)中文仿單未有 HLH 不良反應敘述，但是有血液及淋巴系統異常及 SJS 或 DRESS 的風險，後者之症狀有可能會影響 HLH 的診斷結果，尤其是在早期診斷時。

醫療人員注意事項:

1) HLH 被診斷出的時間會影響死亡率，然而其症狀的診斷容易被 DRESS 等嚴重免疫反應混淆，故建議若以下症狀符合八項中的五項，即診斷為 HLH。
   - ✓ Fever and rash
   - ✓ Enlarged spleen
   - ✓ Cytopenias
   - ✓ High levels of blood ferritin
   - ✓ Elevated levels of triglycerides or low blood levels of fibrinogen
   - ✓ Decreased or absent Natural Killer (NK) Cell activity
   - ✓ Elevated blood levels of CD25 showing prolonged immune cell activation
   - ✓ Hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
2) 醫療人員應提醒病人及其照顧者若發生發燒、紅疹、右上腹疼痛或壓痛、皮膚或眼睛變黃、淋巴結腫大、走路困難、視覺異常、癲癇發作或不正常出血等症狀與徵兆，以上情況有可能在服用後數周才會發生，若有發現應儘速回診就醫。
3) 醫療人員若懷疑病人因為使用藥品導致不良反應發生時，請立即線上通報藥物不良反應及登入於藥物過敏/不良反應記錄中。

院內品項：

Lamictal ® (Lamotrigine) 50 mg/tab 樂命達錠

北醫藥物不良反應工作小組　敬啟
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U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal)

Safety Announcement

[04-25-2018] The Food and Drug Administration (FDA) is warning that the medicine lamotrigine (Lamictal) for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. As a result, we are requiring a new warning about this risk be added to the prescribing information in the lamotrigine drug labels.*

The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent fever, usually greater than 101°F, and it can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs.

Lamotrigine is used alone or with other medicines to treat seizures in patients two years and older. It may also be used as maintenance treatment in patients with bipolar disorder to help delay the occurrence of mood episodes such as depression, mania, or hypomania. Stopping lamotrigine without first talking to a prescriber can lead to uncontrolled seizures, or new or worsening mental health problems. Lamotrigine has been approved and on the market for 24 years, and is available under the brand name Lamictal and as generics.

Health care professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. Advise patients to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms:

- Fever and rash
- Enlarged spleen
- Cytopenias
- Elevated levels of triglycerides or low blood levels of fibrinogen
- High levels of blood ferritin
- Hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
- Decreased or absent Natural Killer (NK) Cell activity
- Elevated blood levels of CD25

showing prolonged immune cell activation

Patients or their caregivers should contact their health care professionals right away if they experience any symptom of HLH while taking lamotrigine. HLH can occur within days to weeks after starting treatment. A physical examination and specific laboratory blood tests and other evaluations are used to diagnose HLH. Signs and symptoms of HLH include but are not limited to:

- Fever
- Enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly
- Swollen lymph nodes
- Skin rashes
- Yellow skin or eyes
- Unusual bleeding
- Nervous system problems, including seizures, trouble walking, difficulty seeing, or other visual disturbances

Read the patient Medication Guide, which explains the benefits and risks of lamotrigine, every time you get a new prescription because the information may change. Do not stop taking lamotrigine without talking to your health care professional first as doing so can cause serious problems.

In the 24 years since lamotrigine's 1994 approval, FDA identified eight cases worldwide of confirmed or suspected HLH associated with the medicine in children and adults (see Data Summary). This number includes only reports submitted to FDA± and found in the medical literature, so there are likely additional cases about which we are unaware. We determined there was reasonable evidence that lamotrigine was the cause of HLH in these eight cases based on the timing of events and the order in which they occurred. The patients in these cases required hospitalization and received drug and other medical treatments, with one dying.

We previously communicated safety information associated with lamotrigine in September 2006 (possible association between Lamictal exposure during pregnancy and oral clefts in newborns) and August 2010 (aseptic meningitis warning). Lamotrigine was also covered as part of a May 2009 safety alert concerning suicidal thoughts and behavior with the entire class of anti-seizure medicines.

We urge health care professionals and patients to report side effects involving lamotrigine (Lamictal) and other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*For additional drug label information, search Drugs@FDA: FDA Approved Drug Products.
±The cases were reported to the FDA Adverse Event Reporting System (FAERS).

Facts about Lamotrigine (Lamictal)

- Lamotrigine is used alone or with other medicines to treat seizures in patients two years and older. Use of lamotrigine as a single drug to treat seizures is approved only in patients 16 and older.
- Lamotrigine is also used as maintenance treatment in adults with bipolar disorder to help delay the occurrence of mood episodes such as depression, mania, or hypomania.
- In addition to HLH, lamotrigine can cause a number of other serious adverse reactions already included in the drug label such as:
    - Rashes, including serious rashes that may need to be treated in a hospital and may cause permanent disability or death
    - Serious allergic reactions that may cause problems affecting the blood, liver, and other organs
    - Suicidal thoughts and actions
    - Aseptic meningitis, a serious inflammation or swelling, of the protective membrane that covers the brain and spinal cord
- Less serious side effects may include dizziness, sleepiness, headache, double vision, blurred vision, nausea, vomiting, and loss of coordination.
- Lamotrigine is available as a tablet to be swallowed, a tablet that dissolves on the tongue (Lamictal ODT), a chewable tablet (Lamictal CD), and as an extended-release tablet (Lamictal XR).

Additional Information for Patients

- The medicine lamotrigine (Lamictal), prescribed for seizures and bipolar disorder, has been associated with a rare but very serious reaction in which the body's immune system is excessively activated, called hemophagocytic lymphohistiocytosis (HLH). This can cause severe inflammation, or swelling, throughout the body and lead to hospitalization or death, especially if treatment is delayed.
- This uncontrolled, excessive immune response can lead to damage or failure of many organs and may progress to death.
- HLH can be caused by an underlying genetic disorder or a gene mutation, or it may be triggered by different conditions, including infections, cancer, and autoimmune diseases. In a small number of cases it can be caused by drugs, including lamotrigine.
- FDA is requiring a new warning about the risk of HLH to be added to the prescribing information in the lamotrigine drug labels.
- Do not stop taking your lamotrigine medicine without first taking to your health care professional. Stopping it suddenly can potentially cause uncontrolled seizures, or new or worsening mental health problems.
- Symptoms of HLH have been reported to occur within 8 to 24 days after the first dose is taken. Contact your doctor right away if you have symptoms of HLH at any time while taking lamotrigine.
- Seek medical attention immediately if you experience any symptoms of HLH while taking lamotrigine. Symptoms of HLH include:
    - Fever, usually >101°F
    - Enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly
    - Swollen lymph nodes

    - Skin rashes
    - Yellow skin or eyes
    - Unusual bleeding
    - Nervous system problems, including seizures, trouble walking, difficulty seeing or other visual disturbances
- Talk to your health care professional if you have questions or concerns about lamotrigine.
- Report side effects from lamotrigine (Lamictal) or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Lamotrigine (Lamictal) has been associated with a rare, but serious and life-threatening adverse reaction called hemophagocytic lymphohistiocytosis (HLH), which can lead to multi-organ failure resulting in hospitalization or death, particularly if diagnosis and treatment are delayed.
- Conduct a medical evaluation as soon as suspicious symptoms are reported and discontinue lamotrigine if HLH is suspected, confirming diagnosis with laboratory tests and other studies. Patients with suspected HLH should be evaluated by a hematologist.
- Diagnosis is often complicated because early signs and symptoms are non-specific, including fever and rash, and HLH can be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- FDA is requiring a new warning about the risk of HLH to be added to the prescribing information in the lamotrigine drug labels.
- In the eight cases FDA studied, symptoms of HLH were reported to have occurred within 8 to 24 days following treatment initiation.
- Tell patients about the symptoms of HLH and advise them to seek medical attention immediately if they experience these symptoms during lamotrigine treatment.
- A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms, according to the published international diagnostic criteria for HLH, known as HLH-2004 diagnostic criteria. These include:
    1. Fever
    2. Splenomegaly
    3. Cytopenias affecting ≥ 2 of 3 lineages in the peripheral blood:
        a. Hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L)
        b. Platelets < 100 x 10^9/L
        c. Neutrophils < 1.0 x 10^9/L
    4. Hypertriglyceridemia and/or hypofibrinogenemia:
    a. Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dl)
    b. Fibrinogen ≤ 1.5 g/L
    5. Hemophagocytosis in bone marrow or spleen or lymph nodes
    6. Low or absent Natural Killer (NK) cell activity
    7. Ferritin ≥ 500 µg/L
    8. Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml
- Lamotrigine may cause other serious adverse reactions such as:

    - Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis
    - Multi-organ hypersensitivity reactions and organ failure
    - Suicidal thoughts or actions
    - Aseptic meningitis
- Tell patients that sudden stopping of lamotrigine treatment can potentially cause uncontrolled seizures, or new or worsening mental health problems. Advise them to seek medical attention immediately if they develop any suggestive symptoms to discuss whether stopping Lamotrigine is appropriate.
- Encourage patients to read the patient Medication Guide they receive with their lamotrigine prescriptions, which explains its benefits and risks.
- Report adverse events involving lamotrigine (Lamictal) or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

We identified eight worldwide cases of confirmed or suspected hemophagocytic lymphohistiocytosis (HLH) associated with lamotrigine use in children and adults reported in the FDA Adverse Event Reporting System (FAERS) database and/or the medical literature from December 1994 through September 2017. Two cases occurred in the U.S. and six occurred abroad.

Five cases had confirmed HLH, fulfilling five of the eight HLH-2004 diagnostic criteria. Three cases had suspected HLH, fulfilling four of the eight HLH-2004 diagnostic criteria. The eight cases had signs and symptoms including fever (n=8), thrombocytopenia (n=8), hyperferritinemia (n=8), hypofibrinogenemia (n=5), splenomegaly (n=3), anemia (n=3), hypertriglyceridemia (n=2), low or absent Natural Killer (NK) cells (n=1), and neutropenia (n=1). All eight cases had positive bone marrow biopsies consistent with hemophagocytosis.

All cases were reported to have serious outcomes. All eight reported hospitalization, three reported other serious important medical events, two reported the outcome as being life-threatening, and one reported death. All cases had a plausible temporal relationship with lamotrigine, occurring within 24 days of starting lamotrigine treatment. Doses ranged from 25 mg every other day to 250 mg once daily in the six cases that reported this information. In seven cases, HLH improved after treatment and discontinuation of Lamictal, and one case did not improve and had a fatal outcome. No cases reported rechallenge. Treatment reported in the eight cases included steroids (n=6), intravenous immunoglobulin (n=4), blood products (n=2), and chemotherapy (n=2).

All eight cases reported concomitant medications. None of the concomitant medications are associated with HLH.

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Related Information

- Hemophagocytic Lymphohistiocytosis
- Seizures
- The Facts on Bipolar Disorder and FDA-Approved Treatments
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines

Pediatr Blood Cancer 2007;48:124–131

REVIEW
HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis

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In HLH-94, the first prospective international treatment study for hemophagocytic lymphohistiocytosis (HLH), diagnosis was based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis). In HLH-2004 three additional criteria are introduced; low/absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels. Altogether five of these eight criteria must be fulfilled, unless family history or molecular diagnosis is consistent with HLH. HLH-2004 chemo-immunotherapy includes etoposide, dexamethasone, cyclosporine A upfront and, in selected patients, intrathecal therapy with methotrexate and corticosteroids. Subsequent hematopoietic stem cell transplantation (HSCT) is recommended for patients with familial disease or molecular diagnosis, and patients with severe and persistent, or reactivated, disease. In order to hopefully further improve diagnosis, therapy and biological understanding, participation in HLH studies is encouraged. Pediatr Blood Cancer 2007;48:124–131. © 2006 Wiley-Liss, Inc.

Key words: diagnosis; hemophagocytic lymphohistiocytosis; survival; treatment

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a disease with major diagnostic and therapeutic difficulties. HLH comprises two different conditions that may be difficult to distinguish from one another: a primary [1] and a secondary form [2]. The primary autosomal recessive form, familial hemophagocytic lymphohistiocytosis (FHL), has an estimated incidence of around 1:50,000 live-born children [3]. FHL is a fatal disease with a median survival of less than 2 months after diagnosis if untreated, and that typically has its onset during infancy or early childhood [4]. Despite its name, family history is often negative since the disease is recessive. Importantly, the onset of FHL and bouts of the disease may be triggered by infections [5].

Secondary HLH (sHLH) may develop as a result due to strong immunological activation of the immune system, which may, for example, be caused by a severe infection. sHLH has been described in immunocompromised hosts in association with viral infections, virus-(infection) associated hemophagocytic syndrome (VAHS, or IAHS) [2,6]. However, most patients with sHLH are *not* obviously immunosuppressed. sHLH may also develop during malignancies (malignancy-associated hemophagocytic syndrome, MAHS); it may either be the presenting clinical picture and initially mask an underlying malignancy, or it may develop during the treatment for a known malignancy [2].

In 1991, the Histiocyte Society presented the first set of diagnostic guidelines for HLH [7], and in 1994 the first prospective international treatment protocol (HLH-94) was introduced [8]. The cumulative experiences from HLH-94 and other studies have led to the development of a new treatment protocol presented here, HLH-2004, which includes updated diagnostic and therapeutic guidelines from the Histiocyte Society.

DIAGNOSIS OF HLH

Clinical Presentation

The most typical findings of HLH are fever, hepatosplenomegaly and cytopenias. Other common findings include hypertriglyceridemia, coagulopathy with hypofibrinogenemia, liver dysfunction, elevated levels of ferritin and serum

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transaminases, and neurological symptoms that may be associated with a spinal fluid hyperproteinemia and a moderate pleocytosis [1,4,9,10]. Other, less common, initial clinical findings include lymphadenopathy, skin rash, jaundice, and edema. Spontaneous partial remissions are observed [11]. The onset of the primary (genetic) form is typically during early infancy but presentation in adolescents and adults have also been reported [12].

Histopathological findings include a widespread accumulation of lymphocytes and mature macrophages, sometimes with hemophagocytosis, affecting especially the spleen, lymph nodes (if enlarged), the bone marrow, the liver, and the cerebral spinal fluid (CSF) [13]. In the liver, a histological picture similar to chronic persistent hepatitis is commonly found [7,13]. Other frequent abnormal laboratory findings in HLH are low natural killer (NK) cell activity [14–18], and a hypercytokinemia, in particular elevated soluble interleukin-2 receptor (sIL-2r) levels (sCD25) [18,19] in serum and in the CSF [19,20].

Importantly, it is still often difficult to distinguish between the familial and secondary forms of HLH despite advances regarding molecular diagnosis. Infection-associated forms of HLH may subside spontaneously, but may also be associated with increased mortality [2]. Furthermore, proving an acute infection at onset of symptoms is not of major diagnostic or therapeutic assistance, since not only sHLH but also FHL often feature a triggering infectious agent [5].

Differential Diagnoses

Many conditions can lead to the clinical picture of HLH, including malignancies (leukemia, lymphoma, other solid tumors), infections (viral, bacterial or parasitic), and rheumatoid disorders. In addition, there are diseases which develop a true HLH episode during their clinical course, such as X-linked lymphoproliferative syndrome (XLP), and Chédiak–Higashi and Griscelli (type 2) syndromes [2,7,21–24]. Some differential diagnoses are Langerhans cell histiocytosis (that may be complicated by HLH), lysinuric protein intolerance [25], severe combined immunodeficiency [26], DiGeorge syndrome, and Omenn's syndrome [27].

Viral infections, especially Epstein–Barr virus (EBV), may trigger primary as well as secondary forms of HLH [2]. Patients with severe sHLH due to EBV infections can be treated with this protocol [28]. It is possible that patients presently considered to have sHLH may have some, as yet unknown, subtle, inborn immune defect.

Macrophage activation syndrome (MAS), a serious complication of systemic rheumatoid arthritis and other childhood systemic inflammatory disorders, is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages. It is also a complication of autoimmune diseases in adults. The recognition that MAS belongs to the secondary or reactive hemophagocytic syndromes has led to a proposal to rename it according to the contemporary classification of histiocytic disorders [29]. Moreover, and in the same way as in HLH, it has been shown that in addition to corticosteroids, cyclosporin A (CSA) is also effective in patients with MAS [30].

Diagnostic Guidelines

Guidelines 1991. In 1991, diagnostic guidelines for HLH were presented by the Histiocyte Society, based on common clinical, laboratory and histopathological findings [7]. However, HLH may also have an atypical and insidious course in some patients in whom all criteria are not always fulfilled [7]. Moreover, a number of patients may develop one or more of the diagnostic criteria late during the course of the disease [7,31]. With these concerns in mind and an extended knowledge on clinical and laboratory findings [10,18,19], the diagnostic guidelines have now been revised [32,33].

Guidelines 2004. The five criteria in the 1991 guidelines are still relevant: 1/fever, 2/splenomegaly, 3/cytopenias affecting at least two of three lineages in the peripheral blood, 4/hypertriglyceridemia and/or hypofibrinogenemia, and 5/hemophagocytosis in bone marrow, spleen, or lymph nodes [7]. In addition, three additional criteria have been introduced: 6/low or absent NK-cell activity, 7/hyperferritinemia, and 8/high levels of sIL-2r (Table I). Altogether five of the eight criteria must be fulfilled, but patients with a molecular diagnosis consistent with HLH do not necessarily need to fulfill the diagnostic criteria [32,33].

NK-cell activity is typically low or absent in HLH, and most perforin deficient patients have abnormal NK-cell activity [15–18,34]. Data on ferritin, an important diagnostic parameter [10], were available in 31 of 48 eligible children with familial disease (defined as having an affected sibling), registered in HLH-94 between July 1994 and June 2002, and 26/31 had a ferritin level above 500 μg/L (sensitivity 0.84). Soluble IL-2r (sCD25) also appears to be a valuable serum parameter in the diagnosis of HLH (sensitivity 0.93) [19,32,33].

Molecular Diagnosis

FHL has, in some patients, been shown to be associated with decreased apoptosis triggering [35]. Subsequently, it was shown that one of the underlying gene defect involves mutations in the gene encoding perforin (*PRF*), which account for 20–40% of all affected FHL families and up to 50% in a cohort of North American families [36–38]. Perforin, which is co-localized with granzyme B in granules of cytotoxic cells, is secreted from cytotoxic T lymphocytes and NK cells upon conjugation between effector and target cells. In the presence of calcium it is able to insert (perforate) into the membrane of the target cell, where it polymerizes to form a cell death-inducing pore (reviewed in Reference [39]). It has been suggested that pore formation may lead to

TABLE I. Revised Diagnostic Guidelines for HLH

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (*to be evaluated in all patients with HLH*)
Fever
Splenomegaly
Cytopenias (affecting $\geq$2 of 3 lineages in the peripheral blood):
Hemoglobin $<$90 g/L (in infants $<$4 weeks: hemoglobin $<$100 g/L)
Platelets $<100 \times 10^9$/L
Neutrophils $<1.0 \times 10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides $\geq$3.0 mmol/L (i.e., $\geq$265 mg/dl)
Fibrinogen $\leq$1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin $\geq$500 μg/L
Soluble CD25 (i.e., soluble IL-2 receptor) $\geq$2,400 U/ml

Comments:

(1) If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful.
(2) The following findings may provide strong supportive evidence for the diagnosis: (a) spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein, (b) histological picture in the liver resembling chronic persistent hepatitis (biopsy).
(3) Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, VLDL ↑, HDL ↓.

destruction of target cells by allowing the entry of granzymes, which trigger apoptosis. However, perforin concentrations which are lower than necessary for pore formation, together with granzyme B, may induce targeted cell death. Recent studies suggest that entry of granzyme B into target cells can also occur in a perforin-independent manner, but granzyme alone is not sufficient to induce toxicity [39].

In 2003, it was shown that mutations in the gene *UNC13D* (17q25) also cause FHL [40]. The encoded protein, Munc 13-4, is essential for the priming step of cytolytic granule secretion preceding vesicle membrane fusion and a deficiency results in defective cytolytic granule exocytosis. A third gene defect associated with FHL (*STX11* on chromosome 6q24) was recently identified encoding a protein, syntaxin 11, which is postulated to play a role in intracellular trafficking, although its precise function is not known [41]. Mutations in *UNC13D* and *STX11* affect up to 20 and 10% of FHL patients in various series, respectively [42,43].

In XLP, 60–70% of patients have mutations in the gene *SAP* (SLAM-associated protein), also termed *SH2-DIA* (SH2-domain containing gene 1A) or *DSHP*. This gene, located at Xq25, regulates a protein involved in signal transduction in T and NK cells. In T cells, the protein binds to the Signaling Lymphocyte Activation Molecule (SLAM, known as CDw150) and in NK cells it binds to 2B4, an NK-cell-activating receptor [21]. Chédiak–Higashi syndrome is linked to the *LYST*-gene (lyzosomal trafficking regulator gene, 1q42), and Griscelli syndrome type 2 is linked to mutations in *RAB27a*, a key effector of cytotoxic granule exocytosis [24].

TREATMENT OF HLH

Therapeutic Background

The first major achievement in the treatment of HLH came when the use of the epipodophyllotoxin derivatives etoposide, and later teniposide, in combination with steroids were shown to induce prolonged symptomatic resolution [44–46]. The immunosuppressive drugs CSA and antithymocyte globulin (ATG) are also effective in FHL [47]. In HLH-94, etoposide and dexamethasone were combined with CSA [8,48].

Cerebral involvement may cause severe and irreversible damage [43,49,50]. In children with HLH, CNS disease at diagnosis often resolves with systemic therapy. Therefore, systemic therapy including dexamethasone, which penetrates the blood-brain barrier better than prednisolone, was first line therapy in HLH-94, and also in cases of CNS involvement. Intrathecal methotrexate was added after 2 weeks in children with progressive neurological symptoms or if an abnormal CSF had not improved.

However, although chemo-immunotherapy is effective in prolonging survival, in some patients more than 5 years after onset [11], it has not been possible to ultimately cure any child with FHL with chemo-immunotherapy alone. It was therefore a major therapeutic advance when allogeneic hematopoietic stem cell transplantation (HSCT) was shown to provide cure for FHL [51–53].

In HLH-94, the estimated 3-year probability of survival overall in HLH-94 at a median follow-up of 3.1 years was 55% (95% confidence interval ±9%) (±9%) (n = 113) [48]. In children with an affected sibling, that is familial disease, the 3-year probability of survival was 51% for eligible patients recruited during the 4-year period, July 1994–June 1998 [48].

Proposed Revision of HLH-94 Protocol

Since the pre-HSCT therapy was successful in allowing as many as 80% of the patients with verified familial disease, that is with an affected sibling, to survive to HSCT, the revised protocol was based on the achievements made by HLH-94 [48]. In addition, minor revisions are included, as presented below.

Initial therapy (weeks 1–8). Not surprisingly in a disease characterized by severe cytopenias and an immunodeficiency, dose modifications in HLH-94 were common. In particular, the doses of VP-16 were decreased in a substantial number of the patients. For dexamethasone, the amount administered was often increased during the induction phase.

During the first 4 years of HLH-94, six patients were reported to have died during the first month of treatment and six more during the second month of treatment. It was sometimes difficult to clarify whether death was caused by the disease or by its treatment, in particular in case of infections associated with neutropenia. However, most deaths were considered to be due to the HLH disease by the reporting physicians. Because of the data cited above, it was proposed that treatment intensity be increased during the first 2 months of therapy with a drug that does not induce myelotoxicity. As a result, in HLH-2004 CSA is initiated upfront instead of after 8 weeks.

Continuation therapy. Of the six children who died during weeks 9–24 on the HLH-94 protocol, all were reported as death due to HLH disease, and at least three of these children had CNS-involvement. We considered including CSF analysis every fourth week in all children (at least for cells and protein, and cytospin in case of CSF pleocytosis) in order to detect early reactivation in the CNS. As a minimum, it is recommended to perform CSF analysis at the time of systemic reactivation or new onset or reactivation of neurological symptoms. Brain MRI is also recommended at diagnosis in these situations.

Intrathecal therapy. With available HLH-94 data, it has not yet been possible to determine whether intrathecal therapy, in addition to the systemic HLH-94 therapy, is beneficial or not. Systemic therapy, as provided in HLH-94, will in most patients reduce CNS disease activity. It cannot be ruled out that intrathecal therapy may have additional beneficial effects, at least in some patients, but potential side-effects also have to be considered [46,48,54,55]. Intrathecal therapy is recommended for patients with signs of persistent active CNS disease and in cases of CNS reactivation. As in HLH-94, up to four intrathecal doses are recommended weeks 3–6, if the neurological symptoms are progressive during the first 2 weeks or if an abnormal CSF at onset has not improved after 2 weeks. With the potential beneficial effect of systemic corticosteroids in mind, it is now suggested to add corticosteroids to the intrathecal therapy.

Hematopoietic cell transplantation. The estimated overall 3-year probability of survival after HSCT for HLH-94 patients recruited during the period 1995–2000 was 64% (CI = ± 10%) (n = 86); 71 ± 18% with matched related donors (n = 24), 70 ± 16% with matched unrelated donors (n = 33), 50 ± 24% with family haploidentical donors (n = 16), and 54 ± 27% with mismatched unrelated donors (n = 13) [56]. The HLH-94 results also suggest that some degree of disease activity at the time for transplantation should not automatically preclude HSCT [56]. The recommended dosages for chemotherapy used in the preparative regimen and the graft-versus-host-disease (GVHD) prophylaxis have been modified slightly in the HLH-2004 protocol to reflect more recent HSCT experience.

HLH-2004 Study Design

The HLH-2004 protocol is designed for the patients with HLH, with or without evidence of familial or genetic disease, regardless of suspected or documented viral infections. The Japanese experience has demonstrated that patients with EBV infection and a clinical picture of HLH have a significant advantage when treated according to this approach [57]. Initial therapy (weeks 1–8) is based on etoposide, dexamethasone, and CSA; only selected patients will receive intrathecal therapy with methotrexate and prednisolone. For a general overview of the patient treatments options in HLH-2004, see Figure 1.

In patients without a known family history who achieve complete resolution of the disease after 8 weeks of therapy, treatment is stopped in order to avoid HSCT in a child that may have sHLH. All children with familial disease or with a diagnosis verified by genetic testing, as well as children with a non-familial disease that is severe and persistent, or reactivated, are recommended to receive continuation therapy with etoposide, dexamethasone, and CSA. HSCT should be performed as early as possible, when an acceptable donor is available.

Patients less than 18 years of age at onset of therapy who fulfil the diagnostic criteria of HLH, and who have not received prior cytotoxic or CSA treatment for HLH, are eligible to be enrolled. Patients with HLH aged 18 years or more and patients who do not fulfil the diagnostic criteria will be studied separately. Similarly, patients with XLP, Chediak–Higashi syndrome, Griscelli syndrome type 2, as well as patients with MAS secondary to known rheumatoid diseases, may be registered and will be studied separately.

Initial therapy. The initial therapy covers the first 8 weeks of treatment (Fig. 2). The complete protocol is available for request at www.histio.org/society/protocols. Maximal initial supportive care is suggested, and appropriate broad-spectrum antibiotics (until culture results) are made available. The supportive therapy includes prophylactic cotrimoxazole, an oral antimycotic during the initial therapy, consideration of antiviral therapy in patients with ongoing viral infections, and IvIG (0.5 g/kg IV) once every 4 weeks (during the initial and continuation therapy). Gastroprotection with ranitidine or some other gastroprotective agent is also suggested. If there is clinical evidence after 2 weeks of progressive neurological symptoms or if an abnormal CSF (cell count and protein) has not improved, 4 weekly intrathecal injections are recommended [46,48,54].

Continuation therapy. Patients without a family history of HLH and without genetic evidence of the disease are

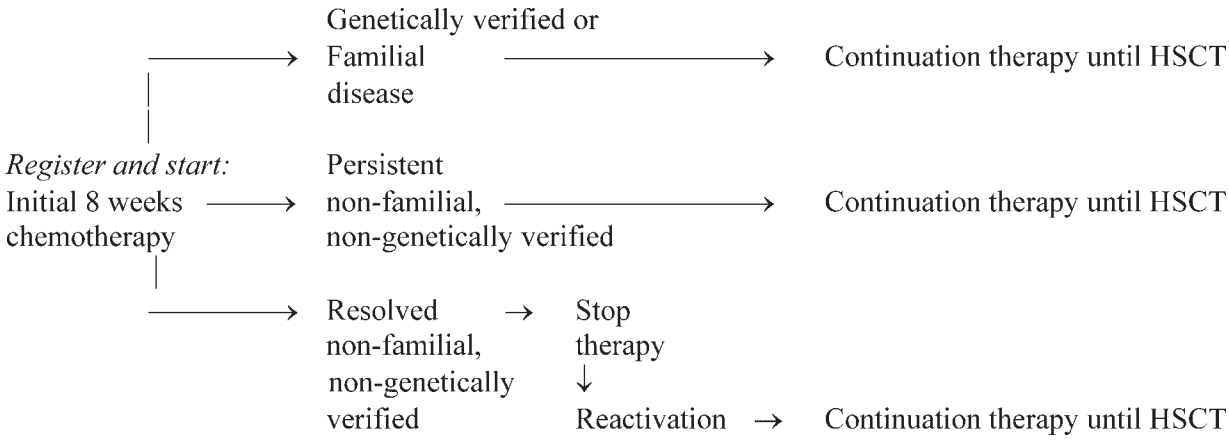

Fig. 1. Flow-sheet of treatment options for children with hemophagocytic lymphohistiocytosis in HLH-2004. If there is a treatable infection it should be treated but be aware that this may not be sufficient and the patient may need HLH-treatment in addition. If HLH is persistent or recurring consider that the patient may have an undiagnosed inherited disease. HLH may also develop secondary to a number of other diseases as malignancies, rheumatic diseases, and metabolic disorders, requiring a different treatment. Start therapy if the patient has a genetically verified disease, a familial form of HLH, or if the disease is severe, persistent, or recurrent. (HSCT = hematopoietic stem cell transplantation.)

recommended to start continuation therapy if the disease is active after the initial therapy. Increasing disease activity may make it necessary to intensify the treatment in some children (see below).

Reactivation therapy. FHL is characterized by frequent reactivations, or even more or less continuous disease activity. In particular, reactivation of the disease is common as therapeutic intensity is reduced, such as during the later part of the initial therapy. Accordingly, a reactivation will commonly respond to an intensification of the initial therapy. Reactivations may also occur following immune response triggering, such as infections and vaccinations. In cases of reactivation, broad-spectrum antibiotics, antiviral therapy, and antifungal therapy should also be considered as supportive or therapeutic measures.

If the patient develops a reactivation, intensification of therapy is recommended, such as to restart from week 2, in which case the initial therapy may be less than 8 weeks, and then continue with modified continuation therapy. Intrathecal therapy is recommended in cases of CNS-reactivation [46,48,54]. HSCT has high priority.

Salvage therapy. The HLH-2004 protocol does not include a salvage protocol. We want to mention an alternative approach of inducing remission, with a regimen including a treatment with steroids, CSA, and ATG [47]. However, in our experience ATG usually fails in patients that are non-responders. It is therefore suggested that salvage therapy is discussed with the local sub-center. Note that early after HSCT, the immunodysregulation may induce a sHLH picture, which may be related to engraftment but delayed

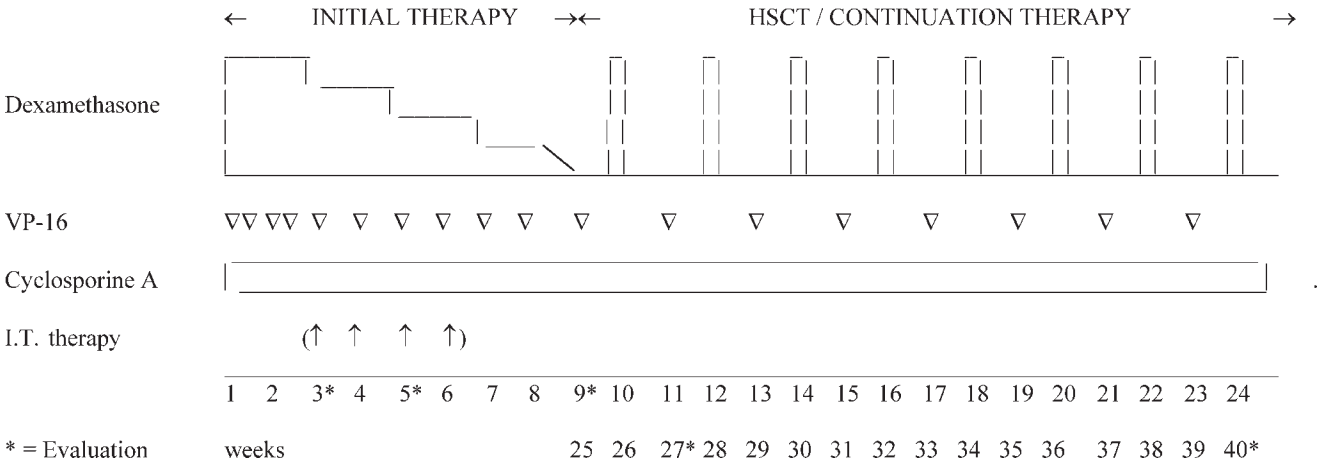

Fig. 2. Schematic treatment overview of the HLH-2004 protocol. For information on whether to start continuation therapy and perform stem-cell transplantation, see text and Figure 1. The complete protocol is available for request at www.histio.org/society/protocols. (VP-16 = etoposide, I.T. therapy = intrathecal methotrexate and corticosteroids, HSCT = hematopoietic stem cell transplantation.)

lymphocyte recovery, necessitating reinstitution of some form of HLH therapy [56].

Stopping therapy. Stopping therapy is only recommended in children with complete resolution of the disease. Close follow-up is warranted, including evaluation for fevers, hepatosplenomegaly, neurological abnormalities, anemia, thrombocytopenia, neutropenia, as well as elevation of ferritin, serum transaminases, and sCD25.

Hematopoietic Cell Transplantation

The choice of the donor rests with the treating physician. If an HLA-identical relative is not available, a matched unrelated donor is recommended. The risk of a sibling carrying the disease must be considered. If a genetic marker (such as for *PRF*, *UNC13D*, or *STX11*) is not available, NK-cell activity can be considered as a surrogate marker of immune dysfunction, although healthy siblings may also have persistently decreased NK-cell activity [16].

If there is no matched donor available, use of a partially mismatched donor is sought. Outcome in the HLH-94 study with regard to various donors has been presented [57]. Results with mismatched donors are improving [52,53,56,58,59]. If no other donor is available, HSCT with a haplo-identical family donor is suggested. The use of peripheral blood or cord blood HSCT may be considered, at the discretion of the physician.

Preparative regimen and GVHD prophylaxis. The preparative regimen for HSCT and the GVHD prophylaxis rests with the transplantation unit, but a suggested regimen is provided. It proposes including etoposide, in addition to busulfan and cyclophosphamide, in the conditioning regimen, in accordance with previous experiences [48,53]. The dosages suggested are outlined in the complete protocol, available for request at www.histio.org/society/protocols. The marrow infusion is preferably made with $\geq 3 \times 10^8$ nucleated cells/kg, and non-T-cell-depleted. In haploidentical and antigen mismatched unrelated transplants, T-cell-depletion may need to be considered. Since there is evidence that donor T cells and NK cells are instrumental in curing HLH, use of T-cell-depletion should be carefully weighted. The GHVD prohylaxis for unmanipulated T-cell replete grafts is based on CSA and a short course of methotrexate, and methotrexate may be substituted by mycophenolate mofetil. Additional treatment for unrelated donor transplants include ATG [53].

Reduced intensity conditioning. There are limited data available on reduced intensity conditioning in HLH [59]. It is not yet possible to make definitive suggestions regarding the preference for such regimens in HLH.

BIOLOGICAL STUDIES

HLH-94 had a number of associated biological studies, including analyses of NK-cell and T-cell cytotoxicity, preparation of DNA for genetic analyses, as well as EBV-associated studies. These studies have all been successful and they have improved diagnostics and therapy, and increased the biological understanding of the disease as well as of normal human immune modulation.

Recent studies have shown that the disease is associated with decreased apoptosis triggering [35,39]. This causes the defect in the NK and T-cell cytotoxicity that has been recognized for long [15,16], with three causative gene defects known today; *PRF* [9], *UNC13D* [40], and *STX11* [41]. It is possible to identify a cohort of individuals with *PRF* gene mutations by the use of flow cytometry for the perforin protein [17]. Moreover, it has also recently been shown that the cytotoxicity defect can be grouped in four subtypes [18], and that group 3 patients will most likely need a HSCT in order to survive [34].

The biological studies in HLH-2004 address these recent novel findings. The goals are to: (1) gather biological material in order to identify additional genetic defects; (2) study the correlation of genetic mutations and associated flow cytometry results; (3) study genotype–phenotype associations; (4) and study the biological and clinical significance of cytotoxic subgroups. It is therefore recommended that study patients be analyzed for genetic mutations, by flow cytometry, and for NK and T-cell cytotoxicity.

CONCLUSION

Survival for patients with HLH has improved dramatically during the last decades as has the understanding of the underlying biological mechanisms. The HLH-94 treatment protocol has been widely accepted, and patients from 29 countries have been registered in the database. Based on the cumulative experiences from HLH-94 and other studies, a new treatment protocol, HLH-2004, has been developed which includes diagnostic and therapeutic guidelines. In order to attempt to further improve diagnosis, therapy and biological understanding, participation in HLH clinical trials is encouraged.

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Lamotrigine(Lamictal)療法可能引起皮膚副作用，通常在開始治療的 8 週內出現。大多數皮疹都很輕微且具有自限性，但也有發生嚴重需住院治療並停止使用本藥的報導，包括致命危險之皮疹如 Stevens-Johnson 徵候群(SJS)及毒性表皮壞死性溶解(TEN)(參閱不良反應)。但也有個案發生在延長治療時，例如 6 個月之後，因此治療期之皮疹發生風險不能依賴早期皮疹之出現推論。在給予推薦劑量 Lamictal 的試驗中，成人發生嚴重皮疹的比率在癲癇病患約為 1/500，其中約有一半(1/1000)被報告是 SJS。

在以雙極性疾患的患者為對象的臨床試驗中，發生嚴重皮疹的機率接近 1/1000。

兒童發生皮疹的危險性比成人更高。研究資料指出，兒童癲癇患者因皮疹住院治療的比率約為 1/300 至 1/100。

兒童的皮疹早期表現可能被誤診為感染。病童若在開始 Lamictal 治療的 8 週內，出現皮疹及發燒的症狀，醫師應考慮藥物反應的可能性。

定性與定量組成

50 毫克錠劑/100 毫克錠劑

劑型

錠劑

臨床特性

【適應症】

癲癇(泛發性強直陣攣性發作及簡單性或複雜性局部發作)成人與 12 歲以上兒童之單獨用藥治療；成人與 2 歲以上兒童之輔助性治療。

Lennox-Gastaut Syndrome 徵候群之治療。

處於明顯鬱期之雙極性疾患情感症狀之治療，有明顯鬱期或鬱-躁期循環之雙極性疾患之情感症狀之預防。

【劑量與用法】

Lamictal 錠劑應整粒吞服，不可咀嚼或壓碎。

若計算出的劑量無法分成數個較低劑量的錠劑，例如使用於兒童(限癲癇)或是肝損傷病患，則給予的劑量則是最接近較低效力的整錠劑數。

再開始的治療

無論因任何原因中止 Lamictal 治療的患者，再次使用本藥時，開處方者須評估是否需要提升至維持劑量，因為高起始劑量及超過建議劑量的 Lamictal 的劑量提升可能引起嚴重的皮疹(參閱警語及注意事項)。當停藥的時間愈久，提升至維持劑量就必須更慎重的考量。當停藥時間超過 5 個半衰期(參閱藥物動力學)，Lamictal 就必需根據適當的進度表來提升至維持劑量。

除非使用本藥的利益明顯的大於可能的風險，否則建議曾因皮疹停用本藥的患者，不要再次使用本藥。

※癲癇

當併用的其他抗癲癇藥物被停掉而採 Lamictal 單獨治療，或在包含 Lamictal 的治療中加入其他抗癲癇藥物時，應考量對 lamotrigine 藥物動力學的影響。(參閱藥物交互作用)

單一療法劑量

- 成人及 12 歲以上(見表一)：

初劑量為 25 mg，每日一次，持續二週；接著改為 50 mg，每日一次，持續二週。隨後增加劑量，每 1-2 週最多增加 50-100 mg，以達到預期的療效。一般維持劑量為每日 100-200 mg，每日一次或分兩次服用。有些患者需要 500 mg/日的劑量，才能達到理想的反應。

- 2-12 歲兒童：

沒有適當的研究提供足夠充分的證據去定義 12 歲以下兒童單獨使用本藥。

癲癇已使用其他藥劑時再增用本藥之劑量

- 成人及 12 歲以上(見表一)：

正在服用 valproate 的患者，不論有無併服其他抗癲癇藥(AED)，Lamictal 的初劑量為每隔天服用 25 mg，持續二週；接著每日服用 25 mg，持續二週。隨後每 1-2 週最多增加 25-50 mg，以達到適當的反應。一般維持劑量為 100-200 mg/日，每日一次或分兩次服用，以達適當的療效。

服用抗癲癇藥或其它會誘導 lamotrigine 醛糖酸化藥物(參閱藥物交互作用)的患者，不論有無併服其他抗癲癇藥(除了 valproate 以外)，Lamictal 的初劑量為 50 mg，每日一次，持續二週；接著每日 100 mg，分兩次服用，持續二週。

隨後每 1-2 週最多增加 100 mg，以達到適當的療效。一般維持劑量為每日 200-400 mg，分兩次服用。

有些患者需要 700 mg/日的劑量，才能達到預期的療效。

服用其它不會顯著抑制或誘導 lamotrigine 醛糖酸化藥物的患者(參閱藥物交互作用)，Lamictal 的初劑量為每天一次服用 25 mg，持續二週；接著每日一次服用 50 mg，持續二週。隨後每 1-2 週最多增加 50-100 mg，直到達到最佳的反應。一般達到最佳反應的維持劑量為 100-200 mg/日，一次或分兩次服用。

表一：推薦使用於成人及 12 歲以上的癲癇治療方法

治療方法	週數 1-2	週數 3-4	維持劑量
單一藥物治療	25 mg (每日一次)	50 mg (每日一次)	100-200 mg(每日一次或分兩次服用)，每一到二週增加 50-100 mg，以達到維持劑量。
已使用 Valproate±其他併用藥物	12.5 mg (隔日服用 25 mg)	25 mg (每日一次)	100-200 mg(每日一次或分兩次服用)，每一到二週增加 25-50 mg，以達到維持劑量。

未使用 Valproate	與下列藥物併用時： Phenytoin Carbamazepine Phenobarbitone Primidone 或其他 lamotrigine 醛糖酸化誘導劑(參閱藥物交互作用)	50 mg (每日一次)	100 mg (分兩次服用)	200-400 mg(分兩次服用)，每一到二週增加 100 mg，以達到維持劑量。
	與其它不會顯著抑制或誘導 lamotrigine 醛糖酸化藥物一起使用時(參閱藥物交互作用)	25 mg (每日一次)	50 mg (每日一次)	100-200 mg(每日一次或分兩次服用)，每 1-2 週增加 50-100 mg，以達到維持劑量。
服用現尚不知是否會與 Lamictal 發生藥動學交互反應的抗癲癇藥之患者(參閱藥物交互作用)，應遵照與 valproate 併用的推薦劑量方法服藥。				

為了減少發生皮疹的風險，必須不能超過初始劑量與隨後之推薦增量(參閱警語及注意事項)

- 2-12 歲兒童(見表二)：

正在服用 valproate 的患者，無論有無併服其他抗癲癇藥(AED)，Lamictal 的初劑量為 0.15 mg/kg 體重/日，每日一次，持續二週；接著 0.3 mg/kg/日，每日一次，持續二週。隨後每 1-2 週最多增加 0.3 mg/kg，以達到適當的反應。一般維持劑量為 1-5 mg/kg/日，單次或分兩次服用，最高劑量為 200 mg/日。

服用抗癲癇藥或其它會誘導 lamotrigine 醛糖酸化藥物(參閱藥物交互作用)的患者，無論有無併服其他抗癲癇藥(除了 valproate 以外)，Lamictal 的初劑量為 0.6 mg/kg 體重/日，分兩次服用，持續二週；接著 1.2 mg/kg/日，分兩次服用，持續二週。隨後每 1-2 週最多增加 1.2 mg/kg，以達到適當的反應。一般維持劑量為每日 5-15 mg/kg，分兩次服用，最高劑量為 400 mg/日。

服用其它不會顯著抑制或誘導 lamotrigine 醛糖酸化藥物的患者(參閱藥物交互作用)，Lamictal 的初劑量為 0.3 mg/kg 體重/日，每日一次或分兩次服用，持續二週；接著服用 0.6 mg/kg/日，每日一次或分兩次服用，持續二週。隨後每 1-2 週最多增加 0.6 mg/kg，直到達到最佳的反應。一般達到最佳反應的維持劑量為 1-10 mg/kg/日，每日一次或分兩次服用，但最多不超過 200 mg/日。

為了確保治療劑量之維持，須監測兒童之體重，當體重有改變時須重新評估劑量。

表二：推薦使用於 2-12 歲兒童的癲癇合併治療方法(每日總劑量：mg/kg 體重/日)

治療方法	週數 1-2	週數 3-4	維持劑量
已使用 Valproate±其他併用藥物	0.15 mg/kg* (每日一次)	0.3 mg/kg (每日一次)	每一到二週增加 0.3 mg/kg，以達到維持劑量 1-5 mg/kg(每日一次或分兩次服用)，最多不超過 200 mg/日。

未使用 Valproate	與下列藥物併用時： Phenytoin Carbamazepine Phenobarbitone Primidone 或其他 lamotrigine 醛糖酸化誘導劑(參閱藥物交互作用)	0.6 mg/kg (分兩次服用)	1.2 mg/kg (分兩次服用)	每一到二週增加 1.2 mg/kg，以達到維持劑量 5-15 mg/kg(每日一次或分兩次服用)，最多不超過 400 mg/日。
	與其它不會顯著抑制或誘導 lamotrigine 醛糖酸化藥物一起使用時(參閱藥物交互作用)	0.3 mg/kg (每日一次或分兩次服用)	0.6 mg/kg (每日一次或分兩次服用)	每一到二週增加 0.6 mg/kg，以達到維持劑量 1-10 mg/kg(每日一次或分兩次服用)，最多不超過 200 mg/日。
服用現尚不知是否會與 lamotrigine 發生藥動學交互反應的抗癲癇藥之患者(參閱藥物交互作用)，應遵照與 valproate 併用的推薦劑量方法服藥。 若對於併服 valproate 的患者所計算出的每日劑量是 1-2 mg 時，則在最初兩週，以隔日服用 2 mg Lamictal 的方式服藥。若對於併服 valproate 的患者所計算出的每日劑量小於 1 mg 時，則不應給予 Lamictal。				

因為有發生皮疹的危險性，所以不可超過初始劑量與隨後之推薦增量(參閱警語及注意事項)。

2-6 歲患者可能需要較高的維持建議劑量。

- 2 歲以下兒童：

尚未有 Lamotrigine 單一療法的研究於 2 歲以下兒童；亦沒有 1 個月以下兒童使用合併療法的研究。Lamotrigine 合併療法治療 1 個月至 2 歲兒童的癲癇局部發作之安全性及療效性尚未建立。因此，Lamictal 不建議使用於 2 歲以下兒童。

※雙極性疾患

- 成人(18 歲以上)：

因為可能會有發生皮疹之風險，需注意不可超過初始劑量與接下來之推薦增量方法。(參閱警語及注意事項)

必須遵照以下的療程轉變方法。此療程包括增加 Lamictal 的劑量直到穩定維持劑量超過 6 週(見下面表三)，在臨床指出其他精神病用藥和/或抗癲癇用藥可以停用之後(見表四)。

表三：治療成人(18 歲以上)雙極性疾患之推薦增量劑量到整日維持劑量之方法：

治療療程	第 1-2 週	第 3-4 週	第 5 週	目標維持劑量（第 6 週）**
a）附加 lamotrigine 醛糖酸化抑制劑療法（如:Valproate）	12.5 mg (每隔一天給予 25 mg)	25 mg (每天給藥一次)	50 mg (每天一次或是分成兩次給藥)	100 mg (每天一次或是分成兩次給藥) (每天最大劑量為 200mg)
b) 附加 lamotrigine 醛糖酸化誘導劑療法，未服用抑制劑 如:Valproate 此劑量方法可	50 mg (每天一次)	100 mg (每天分兩次)	200 mg (每天分兩次)	第 6 週 300 mg, 需要時可在第 7 週增至 400mg/天 (每天分兩次)

和下列藥物一同使用： Phenytoin, Carbamazepine, Phenobarbitone, Primidone 或其它 lamotrigine 醛糖酸化誘導劑 (參閱藥物交互作用)				
c) Lamictal 單一藥物治療或附加療法併用像 lithium, bupropion, olanzapine, oxcarbazepine 或其它已知不會顯著誘導或抑制 lamotrigine 醛糖酸化的藥物	25 mg (每日一次)	50 mg (每日一次或每日分兩次)	100 mg (每日一次或每日分兩次)	200 mg (範圍：100-400 mg) (每日一次或每日分兩次)
注意：因為關於病患服用 AEDs 藥物其與 Lamictal 的交互作用仍未知，因此建議要如同 Lamictal 併用 valproate 一樣給予藥物增量。				

**目標穩定劑量視臨床反應而改變。

a) 附加療法併用 lamotrigine 醛糖酸化抑制劑(如:Valproate)：

患者併服醛糖酸化抑制劑(例如 valproate)則 Lamictal 的初始劑量是 25 mg 每隔一天，給藥 2 週，接著 2 週每天給藥 25 mg。在第 5 週時，劑量必須增加至 50 mg 一天給藥或是一天分兩次給藥。一般可達到理想反應的目標劑量是一天一次給藥 100 mg(或是將此劑量分兩次給藥)。然而，劑量可以視臨床反應增加到最大每日劑量 200 mg。

b) 附加 lamotrigine 醛糖酸化誘導劑療法給沒有使用抑制劑如 Valproate 的病患：此劑量方法可和下列藥物一同使用：phenytoin, carbamazepine, phenobarbitone, primidone 及其它已知會誘導 lamotrigine 醛糖酸化的藥物。(參閱藥物交互作用)

在一些現正服用會誘導 lamotrigine 醛糖酸化的藥物且沒有使用 Valproate 的病患，Lamictal 的初始劑量是 50 mg 一天一次,服用 2 週，接著 2 週每天 100 mg 分成一天兩次服用。劑量需在第 5 週時增加到 200 mg/天，分成 2 次服用。劑量在第 6 週可能可以增加到 300 mg/天，然而，從第 7 週起，可投予一般達到明顯反應的目標劑量 400 mg/天，分成 2 次服用。

c) Lamictal 單一藥物治療或附加療法併用像 lithium, bupropion, olanzapine, oxcarbazepine 或其它已知不會顯著誘導或抑制 lamotrigine 醛糖酸化的藥物：

這些服用 lithium, bupropion, olanzapine, oxcarbazepine 並且沒有服用 lamotrigine 醛糖酸化誘導劑或抑制劑的患者，或只服用 Lamictal 單一藥物治

療的患者，初始劑量是 25 mg/天，服用 2 週。接下來 2 週是 50 mg/天(或是將劑量分成一天 2 次使用)。劑量在第 5 週需增加到 100 mg/天。一般可達到明顯反應的目標劑量是 200 mg/天，一天一次或是將劑量分成一天 2 次服用。然而，在臨床試驗中，劑量是在 100-400 mg 的範圍內。

一旦每日目標維持穩定劑量達到後，可考慮停用其他的精神用藥，此時可以參考以下的劑量表來調整 Lamictal 之劑量(見表 4)。

表四：達到全日維持穩定劑量之雙極性疾患成人患者(18 歲以上)，停用併用之精神用藥或是抗癲癇用藥後之 lamotrigine 劑量調整原則：

<table>
<tr><td>治療方法</td><td>第一週</td><td>第二週</td><td>第三週之後*</td></tr>
<tr><td>(a) lamotrigine 醛糖酸化抑制劑(如 Valproate)停藥之後</td><td>加倍穩定劑量，不要超過 100 mg/每週</td><td colspan="2">維持此劑量(200 mg/天)
（將劑量分成 2 次使用）</td></tr>
<tr><td rowspan="3">(b) lamotrigine 醛糖酸化誘導劑停藥之後，依據其原使用劑量。此劑量方法可和下列藥物一同使用：Phenytoin, Carbamazepine, Phenobarbitone, Primidone 或其它 lamotrigine 醛糖酸化誘導劑(參閱藥物交互作用)</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>(c)停用其它精神用藥或是抗癲癇藥物之後，對未服用 lamotrigine 醛糖酸化誘劑導或抑制劑藥物。(包括 lithium, bupropion, olanzapine, oxcarbazepine)</td><td colspan="3">劑量增量達到維持目標劑量(200 mg/天)
(將劑量分成 2 次使用)
(範圍：100-400 mg)</td></tr>
<tr><td colspan="4">注意：若病患服用與 Lamictal 藥物動力學交互作用未知之 AEDs，建議 Lamictal 治療法為持續現有劑量並依據臨床反應調整 Lamictal 的劑量。</td></tr>
</table>

*若需要則劑量可增加到 400 mg/天

(a) 停用附加 lamotrigine 醛糖酸化抑制劑(如 valproate)的療法之後

一旦當 valproate 被停用之後，則 Lamictal 的劑量須增加到原始目標穩定劑量之雙倍並且維持此劑量。

(b) 停用附加 lamotrigine 醛糖酸化促進劑的療法之後，依據原始維持劑量：

此劑量方法可和 phenytoin, carbamazepine, phenobarbitone, primidone 或其它 lamotrigine 醛糖酸化誘導劑(參閱藥物交互作用)一同使用。

當醛糖酸化促進劑停用之後，Lamictal 需逐漸減量超過 3 週。

(c) 停用附加療法之其他與 Lamictal 藥物動力學未有顯著交互作用之精神用藥或是抗癲癇用藥，例如鋰鹽，bupropion, olanzapine, oxcarbazepine。

在停用其他藥物治療之後，劑量增量方法所達到之目標劑量必須維持。

在治療雙極性疾患患者之 Lamictal 達到穩定之每日劑量之後，再增加使用其他藥

物之時，Lamictal 劑量之調整：

目前尚無針對上述情況調整 Lamictal 每日劑量之臨床經驗。然而，基於藥物交互作用研究，可參照以下的建議(見下面表五)

表五：調整雙極性疾患成人患者(18 歲以上)Lamictal 之每日劑量，接著增加之其他藥物治療：

<table>
<tr><td>治療療程</td><td>現在之 Lamictal 穩定劑量 (mg/天)</td><td>第一週</td><td>第二週</td><td>第三週以後</td></tr>
<tr><td rowspan="3">(a)依照原本使用的 Lamictal 劑量來加入 lamotrigine 醛糖酸化抑制劑(如 valproate)的使用。</td><td>200 mg</td><td>100 mg</td><td colspan="2">維持這個劑量(100 mg/天)</td></tr>
<tr><td>300 mg</td><td>150 mg</td><td colspan="2">維持這個劑量(150 mg/天)</td></tr>
<tr><td>400 mg</td><td>200 mg</td><td colspan="2">維持這個劑量(200 mg/天)</td></tr>
<tr><td rowspan="3">(b)對於未使用 valproate 之病患，依照原本使用的 Lamictal 劑量來加入 lamotrigine 醛糖酸化誘導劑。
此劑量方法可和下列藥物一同使用：
Phenytoin, Carbamazepine, Phenobarbitone, Primidone
或其它 lamotrigine 醛糖酸化誘導劑(參閱藥物交互作用)</td><td>200 mg</td><td>200 mg</td><td>300 mg</td><td>400 mg</td></tr>
<tr><td>150 mg</td><td>150 mg</td><td>225 mg</td><td>300 mg</td></tr>
<tr><td>100 mg</td><td>100 mg</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>(C) 增加使用其他不會與 Lamictal 有顯著藥物動力學交互作用之精神用藥或是 AED 藥物像 lithium, bupropion, olanzapine, oxcarbazepine</td><td colspan="4">維持劑量增量達到之目標劑量(200 mg/天)
（範圍: 100-400 mg）</td></tr>
<tr><td colspan="5">注意: 病患服用 AEDs 這些目前與 Lamictal 藥物動力學交互作用尚未清楚之藥物，則建議如同併用 Lamictal 與 valproate 一樣的劑量方式給藥。</td></tr>
</table>

雙極性疾患成人患者停用 Lamictal：

在臨床試驗中，對比對照組，在突然停用 Lamictal 之後，並不會增加副作用的發生率，嚴重度或型態。因此，病患可以不需要以逐漸停用的方式停用 Lamictal。

- 兒童(小於 18 歲)：

Lamictal 不可用於小於 18 歲之兒童與青少年之雙極性疾患(參閱警語及注意事項)。

Lamictal 的安全性與有效性在這一年齡層尚未被建立。因此，也不會有建議劑量。

※特別患者族群的一般建議劑量

- 有服用荷爾蒙避孕藥的婦女

(a) 對已使用避孕藥的婦女，開始給予 Lamictal：

雖然口服避孕藥已知會增加 lamotrigine 的清除率(參閱警語及注意事項、藥物交互作用)，Lamictal 的建議劑量增量方法，並不會只因為使用荷爾蒙避孕藥，就需要調整。劑量增量方法的選擇，要根據是否 lamotrigine 附加使用於 lamotrigine 醛糖酸化抑制劑(如 valproate)，是否 Lamictal 附加使用於 lamotrigine 醛糖酸化誘導劑(如 carbamazepine, phenytoin, phenobarbital, primidone 或 rifampin)，或者 Lamictal 的添加是在沒有服用 valproate, carbamazepine, phenytoin, phenobarbital, primidone 或 rifampin 的情況下(癲癇見表一，雙極性疾患者見表三)。

(b) 對已使用維持劑量 Lamictal 且未使用 lamotrigine 醛糖酸化誘導劑的患者，開始給予荷爾蒙避孕藥：

根據個別患者的臨床反應，Lamictal 的維持劑量有可能需要提升到兩倍之多(參閱警語及注意事項、藥物交互作用)。

(c) 對已使用維持劑量 Lamictal 且未使用 lamotrigine 醛糖酸化誘導劑的患者，停止給予荷爾蒙避孕藥：

根據個別患者的臨床反應，Lamictal 的維持劑量有可能需要減低至 50%(參閱警語及注意事項、藥物交互作用)。

- 老年人(65 歲以上)：

關於老年患者使用 Lamictal 的資料還很有限。迄今無跡象顯示這個年齡層的反應與年輕人不同。不過，治療老年患者仍應謹慎。

- 肝功能不全：

一般而言，中度肝功能不全(Child-Pugh grade B)降低劑量約 50%，重度肝功能不全(Child-Pugh grade C)降低劑量約 75%。增加和維持劑量須根據病患的臨床反應調整(參閱藥物動力學)。

- 腎功能不全：

將 Lamictal 投藥予腎功能不全的病患須特別小心。對於腎衰竭末期病患，Lamictal 之投藥須特別注意。Lamictal 的初始劑量需根據病患之其他抗癲癇藥物，較低之維持劑量對有明顯腎功能損傷的病患可能仍是有效的(參閱警語及注意事項)。要知道更詳細的藥物動力學資訊，請見藥物動力學性質。

【禁忌症】

Lamictal 禁用於已知對 lamotrigine 或對其他成分過敏之患者。

【警語及注意事項】

- 皮疹

Lamotrigine(Lamictal)療法可能引起皮膚副作用，通常在開始治療的 8 週內出現。

大多數皮疹都很輕微且具有自限性，但也有發生嚴重需住院治療並停止使用本藥的報導，包括致命危險之皮疹如 **Stevens-Johnson** 徵候群**(SJS)**及毒性表皮壞死性溶解**(TEN)(**參閱不良反應**)**。

在給予推薦劑量 **Lamictal** 的試驗中，成人發生嚴重皮疹的比率在癲癇病患約為 **1/500**，其中約有一半**(1/1000)**被報告是 **SJS**。

在以雙極性疾患的患者為對象的臨床試驗中，發生嚴重皮疹的機率接近 **1/1000**。

兒童發生皮疹的危險性比成人更高。

研究資料指出，兒童患者因皮疹住院治療的比率約為 **1/300** 至 **1/100**。

兒童的皮疹早期表現可能被誤診為感染。病童若在開始 **Lamictal** 治療的 **8** 週內，出現皮疹及發燒的症狀，醫師應考慮藥物反應的可能性。

皮疹的整體危險性似乎與以下因素有強烈的關連性：

- **Lamictal** 初劑量過高，並超過 **Lamictal** 的推薦增量方法**(**參閱劑量與用法**)**。
- 同時服用 **valproate (**參閱劑量與用法**)**。

對其他抗癲癇藥物曾有過敏或皮疹病史的患者治療時須謹慎，因這些患者在使用 **Lamictal** 後發生非嚴重性皮疹的頻率，是沒有此類病史患者的三倍左右。

如果出現皮疹，應立即評估患者**(**成人與兒童**)**的狀況，除非確定皮疹與藥物無關，否則應立即停止使用 **Lamictal**。除非使用本藥的利益明顯的大於可能的風險，否則建議曾因皮疹停用本藥的患者，不要再次使用本藥。

皮疹也是過敏徵候群的一部分，伴有各種型態的全身症狀，包括發燒、淋巴腺病變、臉部水腫，血液與肝臟異常，及無菌性腦膜炎**(**參閱不良反應**)**。這種徵候群的臨床嚴重性差別很大；雖然極為少見，但仍可能導致瀰漫性血管內凝血**(DIC)**及多重器官衰竭。值得注意的是，在皮疹還不明顯的時候，便可能出現過敏的早期表現**(**如發燒、淋巴腺病變**)**。若出現這類徵象或症狀，應立即評估患者狀況，如果無法確定其他病因，則應停止使用 **Lamictal**。

停藥後無菌性腦膜炎在大部分的案例中是具有可逆性的，但有些案例顯示重新曝露 **lamotrigine** 有復發的可能性，且重新曝露會造成症狀快速的返回且大部分會更嚴重。**Lamotrigine** 不應重新使用於因 **lamotrigine** 所造成的無菌性腦膜炎的病患上且因此症狀而停藥者。

- 自殺風險

癲癇患者可能會出現憂鬱症及**(**或**)**雙極性疾患的症狀，並有證據顯示，在癲癇和雙極性疾患的患者中，出現自殺意圖的風險有升高的現象。

有 **25%**至 **50%**的雙極性疾患患者會試圖自殺至少一次，且不論是否正在使用雙極性疾患藥物**(**包括 **Lamictal)**，他們都可能會出現憂鬱症狀惡化的現象，並**(**或**)**出現自殺的意念與行為**(**自殺意圖**)**。

在使用 **AEDs** 治療各種適應症**(**包括癲癇和雙極性疾患**)**的患者中，曾有出現自殺意念及自殺行為的報告。一項針對隨機、安慰劑對照性 **AEDs (**包括 **lamotrigine)** 試驗所進行的整合分析也顯示，出現自殺之意念與行為的風險會小幅升高。目前並不確知此風險的形成機制，而現有的資料也無法排除 **lamotrigine** 會使風險升

高的可能性。
因此，應監視患者是否出現自殺意念與行為的徵兆。應告知患者(及其照顧者)，如果出現自殺意念與行為的徵兆，應立即就醫。

- 雙極性疾患的臨床症狀惡化

雙極性疾患患者不論是否正服用其他雙極性疾患治療藥物，皆可能因換用其他雙極性疾患的藥物治療(包括 **Lamotrigine**)而使其臨床憂鬱症狀惡化或出現自殘行為、自殺意念(行為)，尤其在開始治療或改變治療劑量之時。
患者服藥期間，患者及其照顧者需被明確告知應嚴密監視患者之臨床症狀的變化(包括是否有新症狀之發生)，尤其曾有自殺行為或意念之高自殺危險性患者，若有上述情況發生時，應立即告知醫護人員。當病人之臨床憂鬱症狀惡化、出現自殘行為、自殺意念(行為)或新症狀發生，尤其是突然發生時，應積極考慮更改治療計畫，包括停用本藥品。

- 荷爾蒙避孕藥

荷爾蒙避孕藥對 **Lamictal** 效力的影響：
Ethinyloestradiol/levonorgestrel(30mcg/150mcg) 的組合，已顯示會增加 **lamotrigine** 的清除率將近兩倍，導致 **lamotrigine** 的血中濃度降低(參閱藥物交互作用)。滴定顯示，多數案例需要較高維持劑量的 **lamotrigine**(兩倍之多)，才能達到最大療效反應。對尚未使用 **lamotrigine** 醛糖酸化誘導劑，但有使用包含一週無活性藥物(即：免服藥週)的荷爾蒙避孕藥的女性，在無活性藥物的這一週，**lamotrigine** 的血中濃度會逐漸短暫的提升。若在無活性藥物的這一週之前或之中，增加 **lamotrigine** 的劑量，則血中濃度會有更大的提升。劑量使用說明，見 **Lamictal** 特殊族群建議劑量與用法。
臨床人員應對在 **lamotrigine** 的療程中開始或停止荷爾蒙避孕藥的婦女，實施適當的臨床處置，並且多數需要做 **Lamictal** 劑量的調整。
其他口服避孕藥及荷爾蒙取代療法尚未被研究，雖然它們可能對 **lamotrigine** 的藥物動力學有類似的影響。
Lamictal 對荷爾蒙避孕藥效力的影響：
對 **16** 個健康的自願者所做的交互作用研究顯示，併用 **lamotrigine** 和荷爾蒙避孕藥(**ethinyloestradiol/levonorgestrel** 組合)，會輕微的增加 **levonorgestrel** 的清除率，並改變血清中 **FSH** 和 **LH** 的濃度(參閱藥物交互作用)。這些改變對卵巢排卵功能的影響不明。然而，不能排除某些患者併用 **Lamictal** 和荷爾蒙避孕藥可能會導致降低避孕效果的可能性。因此，必須指示患者即時報告她們月經週期的變化，例如突然的出血。

- **Lamotrigine** 對於經由有機陽離子載體 **2(OCT 2)**代謝之藥物的影響

Lamotrigine 是一種經由 **OCT 2** 途徑的腎小管分泌抑制劑(參閱藥物交互作用)。這可能會提昇某些以此為主要排出途徑的藥物的血中濃度。不建議合併使用 **Lamictal** 與以 **OCT 2** 代謝且治療指數狹窄(**narrow therapeutic index**)的藥物如 **dofetilide**。

- 二氫葉酸還原酵素

Lamictal 是一種二氫葉酸還原酵素之微弱抑制劑，因此長期治療可能會干擾葉酸鹽代謝。不過，人體使用 **Lamictal** 長達一年，其血紅素濃度、平均血球體積、血清或紅血球細胞葉酸鹽的濃度並未出現明顯的變化；人體使用長達 **5** 年，其細胞葉酸鹽濃度也未發生明顯變化。

- 腎衰竭

研究顯示，末期腎衰竭患者服用 **lamotrigine** 的單次劑量後，其血中濃度並無顯著變化。儘管如此，預料其尿苷酸化物**(glucuronide)**代謝物會蓄積在體內，所以治療腎衰竭患者應小心。

- 正使用其它含 **lamotrigine** 製劑的患者

Lamictal 不可不經醫師同意就使用已經正在使用含有 **lamotrigine** 藥物的病患。

癲癇：

如同其他的 **AEDs**，驟然停用 **Lamictal** 會導致反彈性痙攣發作。除非是安全性考量**(**如皮疹**)**需要立即停藥，否則 **Lamictal** 的劑量需要至少 **2** 星期的時間慢慢減低。

文獻報導指出，包括癲癇連續狀態在內的嚴重抽搐性癲癇，可能會導致橫紋肌溶解、多重器官功能障礙及瀰漫性血管內凝血，有些甚而致命。使用 **Lamictal** 也曾發生類似的案例。

雙極性疾患：

兒童與青少年**(**年齡小於 **18** 歲**)**

罹患重鬱疾患及其他精神疾患的兒童與青少年患者，其自殺想法及自殺行為之危險性的增加與其所接受的抗憂鬱藥物治療有相關性。

【藥物交互作用】

負責 **lamotrigine** 代謝的酶，已被辨識出是 **UDP-glucuronyl transferases**。沒有證據顯示 **lamotrigine** 在臨床上會明顯誘發或抑制肝臟氧化藥物代謝酵素，並且 **lamotrigine** 和經由 **Cytochrome P450** 酶所代謝的藥物似乎並不會發生交互作用。**Lamotrigine** 可能誘導本身的代謝，但此種作用很輕微，並且沒有明顯的臨床影響。

表六：其它藥物對 **lamotrigine** 醛糖酸化的影響**(**參閱劑量與用法**)**

顯著抑制 **lamotrigine** 醛糖酸化的藥物	顯著誘導 **lamotrigine** 醛糖酸化的藥物	不會顯著抑制或誘導 **lamotrigine** 醛糖酸化的藥物
Valproate	**Carbamazepine** **Phenytoin** **Primidone** **Phenobarbitone** **Rifampicin** **Lopinavir/ritonavir** **Atazanavir/ritonavir*** **Ethinyloestradiol/Levonorgestrel Combination****	**Lithium** **Bupropion** **Olanzapine** **Oxcarbazepine** **Felbamate** **Gabapentin** **Levetiracetam** **Pregabalin** **Topiramate**

		Zonisamide **Aripiprazole**

***關於用藥原則，請參閱下文。**

****其他口服避孕藥及荷爾蒙取代療法尚未被研究，雖然它們可能對 **lamotrigine** 的藥物動力學有類似的影響。參閱劑量與用法—在特殊病人群屬的 **Lamictal** 的一般性劑量建議(女性服用荷爾蒙避孕藥的用藥指引)和警語及注意事項—荷爾蒙避孕藥。**

- 與 **atazanavir/ritonavir** 併用

雖然 **atazanavir/ritonavir** 已證實會降低 **lamotrigine** 的血中濃度(參閱藥物交互作用)，但不須單純因為使用 **atazanavir/ritonavir** 就調整 **Lamictal** 的建議劑量增加原則。應遵循建議的用藥原則來增加劑量，其依據為是否在使用 **valproate** (一種 **lamotrigine** 葡萄糖醛酸化抑制劑)或 **lamotrigine** 葡萄糖醛酸化誘導劑的情況下加入 **Lamictal**，或是否在未使用 **valproate** 或 **lamotrigine** 葡萄糖醛酸化誘導劑的情況下加入 **Lamictal**。

對已在使用維持劑量之 **Lamictal** 且未使用葡萄糖醛酸化誘導劑的患者，若要加入 **atazanavir/ritonavir**，可能必須提高 **Lamictal** 的劑量，若是要停用 **atazanavir/ritonavir**，則必須降低 **Lamictal** 的劑量。

- 和其他抗癲癇藥物的交互作用(參閱劑量與用法)

Valproate 會抑制 **lamotrigine** 醛糖酸化，進而減少 **lamotrigine** 的代謝並延長 **lamotrigine** 的半衰期將近兩倍。

某些會誘發肝臟藥物代謝酶的抗癲癇藥物(例如 **phenytoin**、**carbamazepine**、**phenobarbitone** 與 **primidone**)會誘發 **lamotrigine** 的醛糖酸化代謝，增加 **lamotrigine** 的代謝。

服用 **carbamazepine** 的患者併用 **lamotrigine** 之後，曾有發生中樞神經副作用的報導，包括頭暈、步履不穩、複視、視力模糊及噁心等。減低 **carbamazepine** 的劑量後，這些副作用通常會消失。在某一個研究中曾觀察到，對健康成人自願者，**lamotrigine** 和 **oxcarbazepine** 有類似的效應，但並未研究降低劑量的情況。

在一項研究中，對健康成人自願受試者，給予 **200 mg** 的 **lamotrigine** 和 **1200 mg** 的 **oxcarbazepine**，**oxcarbazepine** 不會改變 **lamotrigine** 的代謝，**lamotrigine** 也不會改變 **oxcarbazepine** 的代謝。

在一項健康受試者的研究中，共同施予 **felbamate(1200 mg**、一天兩次)和 **Lamictal(100 mg**、一天兩次持續十天)，顯示 **felbamate** 在 **lamotrigine** 的藥物動力學上並無臨床上的相聯效應。

針對接受 **Lamictal** 的病人，無論有無併用 **gabapentin**，在血漿濃度回溯性的分析中，**gabapentin** 並不會影響到 **lamotrigine** 的廓清率。

在安慰劑控制的臨床試驗，根據藥劑之間的血清濃度來評估 **levetiracetam** 和 **lamotrigine** 的潛在性藥物交互作用。這些數據顯示 **lamotrigine** 不會影響 **levetiracetam** 的藥物動力學，而 **levetiracetam** 亦不會影響 **lamotrigine** 的藥物動力學。

共同施予 **pregabalin(200 mg/**一天三次)時，**lamotrigine** 的穩定狀態濃度並不會被

影響。因而 **lamotrigine** 和 **pregabalin** 間並無藥物交互作用。

Topiramate 對 **lamotrigine** 的血漿濃度並無影響。不過施予 **Lamictal** 會增加 **15%** 的 **topiramate** 濃度。

在一個針對癲癇病人的研究中，共同施予 **zonisamide(200~400 mg/**天**)**和 **Lamictal(150~500 mg/**天**)**三十五天，在 **lamotrigine** 的藥物動力學上並無顯著效應。

雖然報告中其他抗癲癇藥的血中濃度會改變，**lamotrigine** 在控制研究中顯示並不會影響其他併用抗癲癇藥物的血中濃度。在體外試驗中的結果顯示 **lamotrigine** 不會取代其他抗癲癇藥物與蛋白質的結合部位。

- 和其他精神用藥的交互作用**(**參閱劑量與用法**)**

連續六天每天兩次給予 **20** 位健康受試者無水鋰塩**(lithium gluconate)2 g**，同時給予每天 **100 mg** 之 **Lamictal** 不會影響鋰的藥物動力學。

在 **12** 個受試者中，多次口服劑量之 **bupropion** 對於單一劑量之 **Lamictal** 之藥物動力學並無統計上有意義的影響，僅些微增加 **lamotrigine** 葡萄糖苷酸之曲線下濃度。

在一項研究中，對健康成人自願受試者，**15 mg** 的 **olanzapine** 會降低 **lamotrigine** 的 **AUC 24%**和 **Cmax 20%**。一般，這樣程度的影響不預期有臨床重要性。**200 mg** 的 **lamotrigine** 並不影響 **olanzapine** 的藥物動力學。

對 **14** 個健康成人的受試者實驗裡，每天給予多重劑量的 **Lamictal 400 mg**，對單劑量 **2 mg risperidone** 的藥物動力學上並無臨床上顯著的效應。接著併用 **risperidone 2 mg** 和 **lamotrigine**，在 **14** 個受試者中有 **12** 個發現有困倦的症狀，比較單獨施予 **risperidone** 在 **20** 個受試者中只有一人有此症狀，而單獨給予 **Lamictal** 卻無受試者有此症狀。

體外抑制試驗指出 **lamotrigine** 之主要代謝物 **2-N-glucuronide** 之形成受到 **amitriptyline**、**bupropion**、**clonazepam**、**fluoxetine**、**haloperidol**，或是 **lorazepam** 的些微影響。人類肝臟微粒體之 **bufuralol** 代謝數據指出 **lamotrigine** 並不會減少主要經由 **CYP2D6** 排除之藥物之清除率。體外試驗的結果也指出 **lamotrigine** 的清除率並不太會被 **clozapine**、**phenelzine**、**risperidone**、**sertraline** 或 **trazodone** 影響。

- 和荷爾蒙避孕藥的交互作用

荷爾蒙避孕藥對 **lamotrigine** 藥物動力學的影響：

在一項對 **16** 位女性自願受試者所做的研究中，**30 mcg ethinyloestradiol /150 mcg levonorgestrel** 的口服避孕藥組合，導致口服 **lamotrigine** 的清除率增加將近兩倍，造成 **lamotrigine** 的 **AUC** 和 **Cmax** 平均各降低 **52%**和 **39%(**參閱藥物交互作用**)**。**Lamotrigine** 的血中濃度，在服用無活性避孕藥的這一週**(**即：免服藥週**) lamotrigine** 的血中濃度會逐漸的提升。若之前已存在有 **lamotrigine** 劑量濃度，則在無活性藥物的這一週結束時，**lamotrigine** 的血中濃度平均大概會提升到併服避孕藥時的兩倍。參閱劑量與用法—在特殊病人群屬的 **Lamictal** 的一般劑量

建議(女性服用荷爾蒙避孕藥的用藥指引)和警語及注意事項—荷爾蒙避孕藥。

Lamotrigine 對荷爾蒙避孕藥之藥物動力學的影響：

在一項對 **16** 位女性自願受試者所做的研究中，穩定 **300 mg** 劑量的 **lamotrigine** 對口服避孕藥組合中 **ethinyloestradiol** 之成份的藥物動力學沒有影響。觀察到會些許增加 **levonorgestrel** 的口服清除率，導致 **levonorgestrel** 的 **AUC** 和 **Cmax** 平均各降低 **19%**和 **12%**。在研究中，雖然測量黃體激素顯示，這 **16** 位受試者並沒有排卵的荷爾蒙跡象，但測量 **FSH** 和 **LH** 及動情激素的血中濃度，顯示在某些婦女抑制排卵荷爾蒙的效果有些喪失。**Levonorgestrel** 清除率的輕微增加及 **FSH** 和 **LH** 血中濃度的改變，對卵巢排卵功能的影響不明**(**參閱警語及注意事項**)**。**300 mg/**日以外劑量的 **lamotrigine** 的影響尚未被研究，和其他女性荷爾蒙製劑併用尚未被研究。

- 和其他藥物的交互作用

在一項對 **10** 位男性自願受試者所做的研究中，由於 **rifampicin** 會誘發負責醛糖酸化的肝臟酵素，而增加 **lamotrigine** 的清除率，並縮短其半衰期。對於併用 **rifampicin** 的患者，**lamotrigine** 和醛糖酸化誘導劑的使用應遵守建議治療劑量**(**參閱劑量與用法**)**。

在一項健康受試者的研究中，**lopinavir/ritonavir** 約可減少一半 **lamotrigine** 的血中濃度，可能因為 **glucuronidation** 之引導。當患者併用 **lopinavir/ritonavir**，建議同時使用 **lamotrigine** 及 **glucuronidation** 引導劑**(**參閱劑量與用法**)**。

一項針對健康成人志願者所進行的研究顯示，**atazanavir/ritonavir (300** 毫克**/100** 毫克**)**會使 **lamotrigine (**單劑 **100** 毫克**)**的血中 **AUC** 及 **Cmax** 分別降低平均 **32%** 與 **6%**。

體外試驗評估數據指出 **lamotrigine** 對於 **OCT 2** 的影響，顯示 **lamotrigine** 但並非 **N(2)-glucuronide** 代謝物，在臨床上有療效的濃度時是 **OCT 2** 抑制劑。這些數據顯示 **lamotrigine** 為 **OCT 2** 抑制劑，其 IC_{50} 數據為 **53.8** μ**M(**參閱警語及注意事項**)**。

- 與實驗室檢查的交互作用

Lamictal 已被通報會干擾某些使用在快速尿液藥物篩檢檢驗上，造成偽陽性的反應，尤其是苯環利定(phencyclidine, PCP)。應選用較具特異性的化學方法來確認陽性反應。

【懷孕與授乳】

<u>生育力</u>

動物生殖研究顯示，**lamotrigine** 不會損害生育力。

目前尚無有關 **Lamictal** 對人體生育力影響的經驗。

<u>懷孕</u>

上市後的資料記錄了超過 **8,700** 個後來發現懷孕的婦女，在孕期前三個月暴露在 **Lamictal** 單一藥物治療之結果。這些資料並未證實 **Lamictal** 會增加先天性畸形的風險，但曾有報告指出唇腭裂的風險會增加。一項已完成的控制組研究顯示使

用 **lamotrigine** 後相較於其它先天性畸形，唇腭裂的風險並未提高。
併用 **Lamictal** 的多藥物治療數據，尚不足以評估是否其他藥物致畸型的危險性會受併用 **Lamictal** 的影響。
和其他藥物一樣，**Lamictal** 只有在醫師認為治療的潛在利益遠大於危險性時，才能在懷孕期間使用。
懷孕期間生理上的變化可能會影響 **lamotrigine** 的體內濃度和治療效果。曾有報告在懷孕期間 **lamotrigine** 的體內濃度降低。必須確保懷孕婦女在接受 **Lamictal** 治療時有適當的臨床照護。
授乳
曾有報告指出，**lamotrigine**會移行進入人類的乳汁，但所形成的濃度有極大的差異；繼而在嬰兒體內形成的整體**lamotrigine**濃度最高可達到母體濃度的**50%**左右。因此，在某些餵哺母乳的嬰兒中，**lamotrigine**的血中濃度可能會達到可產生藥理作用的程度。
需衡量哺育母乳的利益是否大於對嬰兒可能產生的副作用。

【對駕駛及機械操作能力的影響】
兩項自願受試者研究證實，**Lamictal** 對於精密的視覺運動協調、眼球移動、身體的晃動及主觀的鎮靜作用，均與安慰劑類似。**Lamictal** 臨床試驗曾出現諸如頭暈及複視等神經副作用。因此，病患在駕駛或是操作機械之前應確認 **Lamictal** 治療是否會造成影響。
癲癇
由於患者對於所有抗癲癇藥物的反應具有個別差異，所以應和醫師討論駕駛與癲癇的特定議題。

【不良反應】
從癲癇或雙極性疾患臨床試驗資料所得到的不良反應將依其適應症來劃分。而上市後監測資料所得到的不良反應列於"上市後資訊"。在考量 **Lamictal** 整體安全性時這三個部分都須顧及。
以下是常用來分類副作用的常規：極常見**(≥1/10)**，常見**(≥1/100, <1/10)**，不常見**(≥1/1000, <1/100)**，罕見**(≥1/10,000, <1/1000)**，極罕見**(<1/10,000)**。

- **癲癇：**

下列不良反應是由癲癇之臨床試驗資料所取得，考量 **Lamictal** 整體安全性時應一併看雙極性疾患臨床試驗與上市後之不良反應。
皮膚與上皮組織疾患
極常見：　皮疹
罕　見：　**Stevens-Johnson** 徵候群
極罕見：　中毒性表皮壞死症
在雙盲、增加藥物**(add-on)**的成人臨床試驗中，服用 **lamotrigine** 的患者有 **10%** 出現皮疹，而服用安慰劑的患者有 **5%**出現皮疹；**2%**因皮疹而終止 **lamotrigine** 治療。皮疹的外觀通常為斑丘疹，通常在開始治療的 **8** 週內出現，停用 **lamotrigine**

後即可恢復(參閱警語及注意事項)。
曾經有發生罕見且有嚴重生命危險之皮疹的報導，包括 **Stevens-Johnson** 徵候群及毒性表皮壞死性溶解(**Lyell** 徵候群)。雖然停藥後大多可以復原，但是有些患者發生不可逆的結痂，並且有少數死亡的案例(參閱警語及注意事項)。
皮疹的整體危險性似乎與以下因素有強烈的關聯性：

- **Lamictal** 初劑量過高，並且超過 **Lamictal** 的推薦增量方法(參閱劑量與用法)。
- 同時服用 **valproate** (參閱劑量與用法)。

皮疹也是過敏症候群的一部份，伴隨不同型態之系統性徵狀(參閱免疫系統**)。
<u>血液與淋巴系統疾患</u>
極罕見：　血液不正常(包括嗜中性白血球減少症、白血球減少、貧血症、血栓性栓塞症、全血球減少症、再生性不良貧血、顆粒性白血球缺乏症) 、淋巴結病
血液不正常及淋巴結病可能或不是與過敏徵狀有關(參閱免疫系統**)。
<u>免疫系統疾患</u>
極罕見：　過敏症狀**(包含如下列症狀：發燒、淋巴腺病變、臉部水腫、血液與肝臟異常、瀰漫性血管內凝血(DIC) 、多重器官衰竭)
皮疹也是過敏徵候群的一部分，伴有各種型態的全身症狀，包括發燒、淋巴腺病變、臉部水腫，及血液與肝臟異常。這種徵候群的臨床嚴重性差別很大；雖然極為少見，但仍可能導致瀰漫性血管內凝血(DIC)及多重器官衰竭。值得注意的是，在皮疹還不明顯的時候，便可能出現過敏的早期表現(如發燒、淋巴腺病變)。如果出現這類徵象或症狀，應立即評估患者狀況，如果無法確立其他病因，則應停止使用 **Lamictal。
<u>精神疾患</u>
常　見：　侵略行為、易怒
極罕見：　顏面痙攣、幻覺、困惑混淆
<u>神經系統疾患</u>
極常見：　頭痛
常　見：　困倦、不眠症、頭昏眼花、顫抖
不常見：　運動失調
罕　見：　眼球震顫症
<u>眼部疾患</u>
不常見：　複視、視力模糊
<u>胃腸道疾患</u>
常　見：　噁心、嘔吐、腹瀉
<u>肝膽疾患</u>
極罕見：　肝功能測試上升、肝功能障礙、肝衰竭
肝臟功能障礙常與過敏反應合併發生，但一些例子也發生於並無過敏反應之情

況。

肌肉骨骼與結締組織疾患

極罕見：　類狼瘡反應**(Lupus-like reactions)**

一般症狀與施用部位情形

常　見：　疲倦

- 雙極性疾患：

下列不良反應是由雙極性疾患之臨床試驗資料所得，考量 **Lamictal** 整體安全性時應一併看癲癇臨床試驗與上市後之不良反應。

皮膚及皮下組織疾患

極常見：　皮疹

罕　見：　**Stevens-Johnson** 徵候群

所有以 **lamotrigine** 做的雙極性疾患研究**(**對照組與非對照組**)**中，**lamotrigine** 會造成 **12%**病患產生皮疹。反之，以雙極性疾患病患為對象之控制實驗，病患服用 **lamotrigine** 發生皮疹的比率是 **8%**，而服用安慰劑的病患是 **6%**。

神經系統疾患

極常見：　頭痛

常　見：　不安、困倦、頭昏眼花

肌肉骨骼與結締組織疾患

常　見：　關節痛

一般症狀與施用部位情形

常　見：　疼痛、背部疼痛

- 上市後資訊：

此部分包括通過上市後監測二個適應症所得到的不良反應。考量 **Lamictal** 整體安全性時，這些不良反應須一併與癲癇和雙極性疾患之臨床試驗部分一起看。

皮膚及皮下組織疾患

罕　見：　禿頭

精神疾患

極罕見：　惡夢

神經系統疾患

極常見：　困倦、運動失調、頭痛、頭昏眼花

常　見：　眼球震顫症、顫抖、不眠症

罕　見：　無菌性腦膜炎**(**參閱警語及注意事項**)**

極罕見：　不安、不穩定、運動失調、帕金森氏症惡化、錐體外作用、手指徐動症

曾有報告指出，**Lamictal** 可能會惡化帕金森氏症病患的症狀，也有一些錐體外作用，手足徐動症或舞蹈症的獨立報導，發生於並未患有帕金森氏症之 **lamotrigine** 使用者。

眼部疾患

極常見：　　複視、視力模糊
罕　見：　　結膜炎

胃腸道疾患

極常見：　　噁心、嘔吐
常　見：　　腹瀉

-下列僅見於癲癇

神經系統疾患

極罕見：　　增加痙攣頻率

【過量】

曾有報告急速服用超過 10-20 倍最大治療劑量，包含致命的案例。此一藥物過量狀況導致包括眼球震顫、運動失調、意識不全、癲癇大發作及昏迷等症狀。

治療/服藥過量時，應讓患者入院治療，並且視臨床需要或依國家毒物防治中心的建議給予適當的支持性療法。用藥過量的患者曾出現 QRS 變寬(心室傳導延緩)。

藥理學特性

【藥效學】

ATC Code：N03AX09

作用機轉

藥理研究結果顯示，lamotrigine 是與電壓相關之鈉離子通道的利用依賴型阻斷劑。它以“使用”及“電位”依賴型阻斷的方式，阻斷神經元的持續反覆放電，抑制 glutamate(這種胺基酸是癲癇發作的關鍵)的病理性釋放，並且抑制 glutamate 引發的動作電位。

藥效學作用

在評估藥物對中樞神經系統影響的試驗中，健康自願受試者服用 lamotrigine 240 mg 的結果與安慰劑並無差別；然而 phenytoin 1000 mg 及 diazepam 10 mg 均會顯著減弱精密的視覺運動協調及眼球移動，增加身體的晃動，並產生主觀的鎮靜作用。

在另一項研究中，carbamazepine 600 mg 的單次劑量顯著減弱精密的視覺運動協調及眼球移動，增加身體的晃動及心搏率。然而 lamotrigine 150 mg 及 300 mg 的結果與安慰劑並無差別。

【藥物動力學】

吸收

Lamotrigine 可以迅速且完全地經由腸道吸收，它沒有顯著的首渡代謝。約於口服後 2.5 小時可達到最高血中濃度。餐後服用會略微延後達到最高血中濃度的時間，但不影響吸收量。在最高單次劑量達 450 mg 的試驗中，藥動學性質呈線性關係。穩定狀態最高血中濃度的個別差異很大，但是每個人本身的濃度變化極小。

分佈

Lamotrigine 有 55% 會與血漿蛋白結合；不太可能從血漿蛋白被置換出來而導致中毒。分佈體積為 0.92-1.22 L/kg。

代謝

UDP-glucuronyl 轉移酵素已被確認為代謝 lamotrigine 的酵素。Lamotrigine 會視劑量而適度地誘導自身代謝。但沒有證據顯示，lamotrigine 會影響其他抗癲癇藥物的藥動學性質。而且資料也顯示，lamotrigine 不會與其他經由細胞色素 P450 酵素代謝的藥物發生交互作用。

排除

健康成人的平均穩定狀態廓清率為 39±14 mL/min。Lamotrigine 主要經由代謝，隨後以尿苷酸代謝物的形式由尿液排出體外。低於 10%的藥量以原型從尿液排出。僅約有 2%的藥物相關物質由糞便排出。廓清率與半衰期均與劑量無關。健康成人的平均排除半衰期為 24-35 小時。一項研究顯示，Gilbert 徵候群患者的 lamotrigine 平均廓清率約比正常對照組少 32%，但仍在一般範圍內。

Lamotrigine 的半衰期受併服藥物的影響很大。若給予醛糖酸化誘發劑，如 carbamazepine 及 phenytoin，其平均半衰期約縮短為 14 小時；與 valproate 併服時，則約可延長至 70 小時(參閱劑量與用法、藥物交互作用)。

特殊的患者族群

- 兒童：

兒童的廓清率(以體重校正)比成人高；5 歲以下兒童的廓清率最高。兒童的 lamotrigine 半衰期通常比成人更短；與酵素誘發劑併服時(如 carbamazepine 及 phenytoin)，平均半衰期約縮短為 7 小時；與 valproate 併服時，則約可延長至 45-50 小時(參閱劑量與用法)。

- 老年人：

以包括老年和年輕癲癇病患的族群藥物動力學分析的結果顯示，廓清率的變化並沒有達到臨床上有相關的程度。單一劑量投藥後，20 歲的成人組廓清率為 35 mL/min，而 70 歲的老人組廓清率為 31 mL/min，下降 12%。經過 48 週的治療後，成人組(41 mL/min)與老人組(37 mL/min)之廓清率差異則為 10%。此外，一項以 12 名健康老年人為對象所做的 lamotrigine 藥物動力學研究顯示，單劑量投與 150 mg 之後，老年人之平均廓清率為(0.39 mL/min/kg)，與由不含老年人的 9 個研究中單劑量投與 30 到 450 mg 後所得到的平均廓清率(0.31 到 0.65 mL/min/kg)相比，是在正常範圍內。

- 腎功能不全患者：

12 名慢性腎臟衰竭志願者與其他 6 名正在做血液透析者，分別給予 100 mg 單一劑量之 lamotrigine。CL/F 平均值是 0.42 mL/min/kg(慢性腎衰竭)，0.33 mL/min/kg(介於血液透析)與 1.57 mL/min/kg(正在做血液透析中)，與健康志願者 0.58 mL/min/kg 比較。平均血漿半衰期是 42.9 小時(慢性腎衰竭)，57.4 小時(介於血液透析)與 13.0 小時(正在做血液透析中)，與健康志願者的 26.2 小時作比較。平均而言，大約 20% (範圍在 5.6 到 35.1)體內的 lamotrigine 的量在一個 4 小時血

液透析期之間被排除。對這一類病人而言，lamotrigine 初始劑量必須依據病患之 AED 療程；較低之維持劑量可能對有顯著腎功能不全的病患可能仍是有效的。

- **肝功能不全患者：**

一單一劑量藥物動力學研究，包括 24 個不同程度肝功能不全患者與 12 個健康的受試者作為對照組。顯見之 lamotrigine 清除率中位數在 A,B,C 級(Child-Pugh 分級)病患是 0.31、0.24 或是 0.10 mL/min/kg，而健康對照受試組則是 0.34 mL/min/kg。使用本藥之起始、增量、維持劑量於 B,C 級肝功能不全患者應降低劑量約 50%(B 級)及 75%(C 級)。增量及維持劑量應視臨床反應調整。

【臨床研究】

預防雙極性疾患病患心理症狀的臨床藥效：

成人(18 歲以上)

有兩個重要的研究已經證明預防雙極性疾患Ⅰ型疾病病患之心理症狀。

臨床試驗 SCAB20003 是一個多中心，雙盲，雙啞，安慰劑與鋰鹽對照，隨機固定劑量評估之試驗，針對現在或是曾經經歷重憂鬱症狀之雙極性疾患病患且長期預防其憂鬱症狀之發作。一旦固定使用 Lamictal 單獨治療或是併用其他精神用藥治療，便會將病患隨機分配至一個五種治療方式的群組：Lamictal(50, 200, 400 mg/天)，Lithium(血漿值 0.8~1.1 mEq/L)或是最大值到 76 週(18 月)的對照組。這樣的治療可以維持直到出現憂鬱或是躁狂症狀而被認定需要增加額外的藥理治療或是電療(ECT)。

主要的終點是“產生情緒症狀時插入治療的時間點”(TIME)插入的治療可以是額外的藥理治療或是電療(ECT)。使用三種處理來自插入治療前先停用的病患之數據來分析這個終點。在這些分析中 P 值介於 0.003 到 0.029 之間。在初次憂鬱症狀的時間與初次躁狂/輕躁狂或是混合症狀的時間之支持性分析中，使用 Lamictal 的病患比起對照組在發生初次憂鬱症狀前有較長的時間(P=0.047)而治療不同對於躁狂症/輕躁狂或是混合症狀並無統計學上的意義。

臨床試驗 SCAB2006 是一個多中心，雙盲，雙啞，對照組與鋰鹽控制，隨機性，有彈性的 Lamictal 劑量評估，長期預防曾經有躁狂症狀或是輕躁狂症狀之雙極性 I 疾患病患之躁狂症與/或憂鬱症之復發。

一旦穩定使用 Lamictal 單獨治療或是 Lamictal 加上治療精神異常藥物，病患會隨機被分配到三個治療群中的一個：Lamictal 100 到 400 mg/天，鋰鹽(血漿值 0.8 到 1.1mEq/L)，或是 76 週(8 個月)的對照組。治療的療程持續直到發生新的情緒症狀(憂鬱或是躁狂)被認為需要插入額外的藥理治療或是電療(ECT)。

主要的終點是“產生情緒症狀時插入治療的時間點”(TIME)插入的治療可以是額外的藥理治療或是電療(ECT)。使用三種處理來自插入治療前先停用的病患之數據來分析這個終點。在這些分析中 P 值介於 0.003 到 0.023 間。在初次憂鬱症狀的時間與初次躁狂/輕躁狂或是混合症狀的時間之支持性分析中，使用 Lamictal 的病患比起對照組在發生初次憂鬱症狀前有較長的時間(P=0.015)而治療之不同對於躁狂症/輕躁狂或是混合症狀並無統計學上的意義。

一項綜合此二研究的分析顯示，與安慰劑對照組比較，Lamictal 的患者到第一次憂鬱症狀及躁鬱、輕躁狂及混合症狀前有較長的時間，但此一作用仍以對憂鬱症狀較為明顯。

在臨床試驗中，因為有誘發不穩定性之傾向，躁狂症或是輕躁狂症在 Lamictal 治療上與對照組並無有意義的不同。

【臨床前安全性資料】

在動物中，以超過人類治療劑量進行的生殖毒性試驗並未顯示致畸胎的作用。然而，因 lamotrigine 是一種二氫葉酸還原酵素之微弱抑制劑，當懷孕時使用葉酸抑制劑，理論上仍存在著使胎兒畸形的危險。

廣泛的致突變性試驗結果顯示，lamotrigine 對人類遺傳無危險性。

大鼠及小老鼠的長期研究顯示，lamotrigine 沒有致癌性。

藥劑學特性

【賦形劑】

Tablets:

Lactose

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Iron oxide yellow (E172)

Magnesium stearate

【不相容性】

無報告。

【有效期限】

有效期限標示於包裝上。

【貯存注意事項】

儲存於 30℃以下，避光，保持乾燥。

【容器之性質與內容物】

8-1000 粒盒裝/4-1000 粒盒裝。

【使用及操作說明】

無

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