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(54) Title: SUSTAINED RELEASE FORMULATIONS COMPRISING LAMOTRIGINE

(57) Abstract: A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof and methods of treatment and uses thereof.

SUSTAINED RELEASE FORMULATIONS COMPRISING LAMOTRIGINE

This invention relates to a novel method of treatment using lamotrigine and novel formulations, in particular tablet formulations, for use in such methods.

Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine is disclosed in US 4,602,017 and EP0021121. Products comprising lamotrigine are marketed under the trade name LAMICTAL™ by the GlaxoSmithKline group of companies. Such products are particularly effective for treatment of CNS disorders, particularly epilepsy; pain; oedema; multiple sclerosis and psychiatric indications including bipolar disorder.

Various tablet formulations of lamotrigine have been approved for marketing, for instance, conventional compressed instant release (IR) tablets comprising 25 mg, 50mg, 100 mg, 150 mg or 200 mg of active ingredient. These are administered once, twice or three times daily. For lamotrigine, added to an antiepileptic drug regime containing valproic acid, titration begins at 25 mg every other day for weeks 1 and 2 and increased to 25 mg every day for weeks 3 and 4. After this initial period the maintenance dose of 100 to 400 mg/day can be achieved by increasing the dose by 25 to 50 mg/day. If lamotrigine is added to enzyme-inducing antiepileptic drugs (EIAEDS) without valproic acid the dose is 50 mg/day for weeks 1 and 2 and 100 mg/day in 2 divided doses thereafter. To achieve the maintenance dose of 300 to 500 mg/day in 2 divided doses, doses may be increased by 100 mg/day every 1 to 2 weeks. These regimens provide a therapeutic amount of lamotrigine.

In addition, WO92/13527 (The Wellcome Foundation Limited) describes tablet formulations comprising water dispersible tablets comprising lamotrigine and a dispersing agent where the dispersing agent is a swellable clay such as a smectite and is generally present within the granules of the tablet to provide a tablet which is capable of dispersing in water within 3 minutes to provide a dispersion which will pass through a 710 μm sieve. The tablet can be optionally film coated in which case the dispersion time is less than 5 minutes. Chewable dispersible tablets which may be swallowed whole, chewed or dispersed in a small amount of water are marketed comprising 2mg, 5mg, 25 mg or 100 mg of active ingredient. These are generally administered to paediatric patients.

WO96/17611 (The Wellcome Foundation Limited) discloses pharmaceutical compositions comprising

a) 0.5 to 50% by weight of lamotrigine;
b) from 15 to 50% by weight lactose;
c) from 15 to 50% by weight of starch;
d) from 0.5 to 50% crystalline cellulose; and
e) 5 to 15% by weight of polyvinylpyrrolidone;

and which is in the form of a free flowing powder having the following properties:

(i) no granules having a particle size of greater than 850μm,
(ii) at least 90% by weight having a particle size of 75 to 850 μm,
(iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, 12th edition and

(iv) at least 90% by weight of lamotrigine dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan 12th edition 1991.

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first pass metabolism. The absolute bioavailability is about 98%, which is not affected by food.

The chewable dispersible tablets were found to be equivalent to the lamotrigine compressed IR tablets whether they were administered as dispersed in water, chewed and swallowed or swallowed as whole in terms of rate and extent of absorption.

Other drugs available on the market for the treatment of epilepsy are, but not limited to, carbamazepine (Tegretol TM), valproate (Depakote TM), tiagabine (Gabitril TM), levetiracetam (Keppra TM), gabapentin (Neurontin TM) and phenytoin (Dilantin TM). Carbamazepine is available as an instant release tablet, a time releasing chewable tablet (Carbatrol; extended release beads) or Tegretol-XR an osmotic pump tablet, and a liquid to be administered by mouth. Valproate is available as an instant release tablet and a suspension. In the US valproate is also available as Depakote a delayed release (coated) tablet which contains sodium valproate + valproate in 1:1 formulation and also Depakote ER an extended release form). Gabapentin, tiagabine and levetiracetam are available as instant release tablets. Dilantin is available in a 'kapseal' that modifies release.

Existing marketed tablet formulations of lamotrigine provide immediate release of the active ingredients once the tablet reaches the stomach. The peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The disadvantage is that the plasma concentration (pharmacokinetic profile (PK)) achieved with conventional tablets is cyclical, with peaks occurring after administration followed by troughs occurring before the next administration of drug, see Figure (1).

In particular for the treatment of epilepsy it is speculated that the troughs may lead to breakthrough seizures and the peak plasma concentration may result in some adverse events (AE) occurring in some patients or alternatively the rate of increase in plasma concentration in the initial stages before the peak plasma concentration is achieved may also effect the AE profile.

Until recently, it was not known where, in the gastrointestinal tract, lamotrigine is absorbed. In carrying out a regional absorption study it has recently been discovered that the extent of absorption of lamotrigine is consistent when the drug is delivered to any point in the gastrointestinal tract between the stomach and the ascending colon. The extent of absorption is also equivalent whether the drug is delivered as a solid or as a solution.

Accordingly, in a first aspect, the invention comprises a sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof.

A further aspect of the present invention provides for a method of treating CNS disorders, which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of a sustained release formulation.

A further aspect of the present invention provides for a method of treating CNS disorders, which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof, in the form of a sustained release formulation wherein the lamotrigine or a pharmaceutically acceptable derivative thereof is released approximately 2 to 20 hours after administration, preferably 6 to 16 hours after

administration and more preferably 10 to 15 hours, alternatively 10 to 14 hours after administration.

When used herein the term "CNS disorder" includes epilepsy; pain; oedema, multiple sclerosis, schizophrenia and psychiatric conditions including bipolar disorder, preferably epilepsy; pain; oedema, and psychiatric conditions including bipolar disorder, particularly epilepsy, pain and bipolar disorder.

When used herein the term "pain" includes acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, trigeminal neuralgia, sympathetically maintained pain and pain associated with diabetic neuropathy) and pain associated with cancer and fibromyalgia or pain associated with migraine.

Schizophrenia is a serious psychiatric disease that affects 1% of the world's population. Onset of the disorder occurs typically in the late teens or early 20's and in approximately 80% of cases becomes a lifelong condition. Furthermore, schizophrenia is associated with significant mortality, with 40% of patients attempting suicide within 10 years of the onset of this disorder. The disorder was rated as the 5th leading cause of disability in the US in a joint World Health Organisation – World Bank study in 1996 (Murray and Lopez, 1996).

The clinical presentation of schizophrenia can include positive symptoms, such as hallucinations, delusions, or thought disorder, and negative symptoms such as apathy, avolition, or poverty of speech.

The treatment of schizophrenia relies on the use of anti-dopaminergic drugs following the original discovery in the 1950's of the efficacy and mechanism of action of chlorpromazine. Chlorpromazine and other so-called "typical" antipsychotic drugs are still in common use today, though due to their association with motor side-effects, they are increasingly replaced by the newer "atypical" antipsychotics, such as clozapine (Clozaril^{TM}), olanzapine (Zyprexa^{TM}) or risperidone (Risperdal^{TM}). These newer drugs have a mixed pharmacology which includes dopamine D2 receptor antagonism and antagonism of the 5-HT2a receptor. Despite efficacy and relative safety of these newer drugs, a significant proportion of patients fail to respond to treatment and of those that do, many do not achieve a clinically meaningful improvement in global functioning and quality of life.

In some patients, episodes of major depression, mania, or mixed mania can occur alongside symptoms of schizophrenia. The distinction between schizophrenia and mood disorder is then somewhat blurred and a diagnosis of schizoaffective disorder is often used. Treatment of schizoaffective disorder typically requires a combination of an antipsychotic, an antidepressant, a mood stabiliser, and anxiolytic drugs. Although positive psychotic symptoms can usually be controlled, negative symptoms and affective symptoms are poorly treated by current medications.

Despite 40 years of development there remains a significant unmet need for treatment for patients with the chronic debilitating disorder schizophrenia.

Multiple sclerosis (MS) is an autoimmune disease which is a progressive disease of the central nervous system (CNS) in which patches of myelin (the protective covering of nerve fibres) in the brain and spinal cord are destroyed by the body's own immune system. This destruction leads to scarring and damage to the underlying nerve fibres and may manifest itself in a variety of symptoms, depending on the parts of the brain and spinal cord that are affected. Spinal cord damage may result in tingling or numbness as well as heavy and/or weak feeling in the

extremities. Damage in the brain may result in muscle weakness, fatigue, unsteady gain, numbness, slurred speech, impaired vision, vertigo and the like. Leandri et al (J Neurol(2000) 247:556-558 reported that lamotrigine had been used in the treatment of trigeminal neuralgia secondary to multiple sclerosis.

A further aspect of the invention is the use of lamotrigine or a pharmaceutically acceptable derivative thereof in the treatment of multiple sclerosis.

A further aspect of the invention is a method of treatment of multiple scelrosis which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof.

A further aspect of the invention is the use lamotrigine or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of multiple sclerosis.

When used herein the term "pharmaceutically acceptable derivative" means a salt, ester or salt of such ester which upon administration to the recipient such a human is capable of providing (directly or indirectly) lamotrigine or an active metabolite thereof. Preferred salts are inorganic acid salts such as hydrochloride, hydrobromide, phosphate or organic acid salts such as acetate, fumarate, xinafoate, tartrate, succinate or glutarate.

The term "treatment" as used herein includes the treatment of established disorders and also includes the prophylaxis thereof. This is particularly relevant for epilepsy wherein medication may treat seizures or prevent future seizures from occurring.

As used herein, the term "sustained release" refers to the gradual but continuous release over any extended period of lamotrigine after oral ingestion e.g. 2-20 hours preferably between 6 to 16 hours, and more preferably between 10 and 15 hours, alternatively 10 and 14 hours and which starts when the formulation reaches the stomach and starts to disintegrate/dissolve/erode. The release will continue over a period of time and may continue throughout the small intestine and after the formulation reaches the large intestine.

A further aspect of the invention provides a method of treating CNS disorders which comprises orally administering to a patient a therapeutically effective amount of lamotrigine in the form of a sustained release formulation wherein substantially all the lamotrigine is released from the formulation in the 2 to 20 hours after administration, preferably 6 to 16 hours after administration and more preferably 10 to 15, alternatively 10 to 14 hours after administration.

A further aspect of the invention provides a sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof, wherein substantially all the lamotrigine or a pharmaceutically acceptable derivative thereof is released from the formulation 2 to 20 hours after administration, preferably 6 to 16 hours after administration and more preferably 10 to 15, alternatively 10 to 14 hours after administration.

When used herein "substantially all" means more than 85%, preferably more than 90%.

Administration of lamotrigine over this time period delivers it gradually to the sites where lamotrigine is readily absorbed but with a slower rise in serum concentrations and reduced post-dosing peaks to mitigate dosing related adverse events (AE's) yet provide sufficient minimum plasma/serum concentrations (Cmin) to maintain efficacy. A formulation which achieves an area under the curve (AUC) equivalent to the conventional instant/immediate release (IR) tablet (90% confidence interval (CI) for the geometric least squares (GLS) mean ratio should fall within the range 80-125% compared to the reference IR product) is termed "bioequivalent".

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