AMOGINE®

(Lamotrigine)

ACTION

Lamotrigine, the active ingredient of Amogine, is a use-dependant blocker of voltage gated sodium channels. It produces a use and voltage-dependant block of sustained repetitive firing in cultured neurons and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

INDICATIONS

Epilepsy:

Monotherapy in adults and children over 12 years of age:

1. Simple partial seizures
2. Complex partial seizures
3. Secondarily generalized tonic clonic seizures
4. Primary generalized tonic clonic seizures

Add-on therapy in adults and children over 2 years of age:

1. Simple partial seizures
2. Complex partial seizures
3. Secondarily generalized tonic clonic seizures
4. Primary generalized tonic clonic seizures

Amogine is also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

Bipolar Disorder:

Amogine is indicated for the maintenance treatment of Bipolar Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of Amogine in the acute treatment of mood episodes has not been established. The effectiveness of Amogine as maintenance treatment was established in 2 placebo-controlled trials of 18-month duration in patients with Bipolar Disorder as defined by DSM-IV. The physician who elects to use Amogine for periods extending beyond 18 months should periodically re-evaluate the long term usefulness of the drug for the individual patient.

DOSAGE AND ADMINISTRATION

Epilepsy:

Dosage in monotherapy:

Adults and children over 12 years: The initial Amogine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day as in two divided doses. Some patients have required 500 mg/day of Amogine to achieve the desired response.

Children aged 2 to 12 years: There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years.

Dosage in add-on therapy:

Adults and children over 12 years: In patients taking valproate with/without any other anti-epileptic drug (AED) the initial Amogine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses. In those patients taking enzyme inducing AED's (e.g. phenytoin, carbamazepine, phenobarbitone and primidone) with/without other AED's (except valproate) the initial Amogine dose is 50 mg once a day for two weeks, followed by 100 mg /day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-400 mg/day given in two divided doses. Some patients have required 700 mg /day of Amogine to achieve the desired response. In patients taking AED's where the pharmacokinetic interaction with Amogine is currently not known, the dose escalation as recommended for Amogine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

Children aged 2 to 12 years: In patients taking valproate with/without any other anti-epileptic drug (AED), the initial Amogine dose is 0.2 mg/kg body weight/day given once a day for two weeks, followed by 0.5 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.5-1 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses. In those patients taking enzyme inducing AED's (e.g. phenytoin, carbamazepine, phenobarbitone and primidone) with/without other AED's (except valproate) the initial Amogine dose is 2 mg/kg body weight/day given in two divided doses for two weeks, followed by 5 mg/kg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 2-3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in two divided doses. In patients taking AED's where the pharmacokinetic interaction with Amogine is currently not known, the dose escalation as recommended for Amogine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved. **Note:** If the calculated daily dose is 2.5-5 mg, then 5 mg Amogine may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 2.5 mg, then Amogine should not be administered. It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.

Children aged less than 2 years: there is insufficient information on the use of Amogine in children aged less than 2 years.

Use in the elderly: There is limited information on the use of Amogine in elderly patients. To date, there is no evidence to suggest that the response of this age group differs from that in the young. However, elderly patients should be treated cautiously.

Bipolar Disorder: The target dose of Amogine is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated; however, no additional benefit was seen at 400 mg/day compared to 200 mg/day. Accordingly, doses above 200 mg/day are not recommended. If other psychotropic medications are withdrawn following stabilization, the dose of Amogine should be adjusted. For patients discontinuing valproate, the dose of Amogine should be doubled over a 2-week period in equal weekly increments. For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of Amogine should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements. The dose of Amogine may then be further adjusted to the target dose 200 mg as clinically indicated. If other drugs are subsequently introduced, the dose of Amogine may need to be adjusted. In particular, the introduction of valproate requires reduction in the dose of Amogine.

Note: To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of Amogine should not be exceeded.

Administration: Amogine tablets should be swallowed whole with a little water. To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to body weight, do not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

CONTRAINDICATIONS

Amogine is contra-indicated in individuals with known hypersensitivity to Lamotrigine. Lamotrigine is cleared primarily by metabolism in the liver. No studies have been carried out in patients with significant impairment of hepatic function. Until such data become available Lamotrigine is contra-indicated in this condition.

WARNINGS AND PRECAUTIONS

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of Lamotrigine treatment. The majority of rashes are mild and self limiting, however rarely, serious potentially life threatening skin rashes including Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported.

The approximate incidence of serious skin rashes in adults and children over the age of 12 is 1 in 1000. The risk is higher in children under the age of 12 than in adults.

Available data from a number of studies suggest the incidence in children under the age of 12 requiring hospitalization due to rash ranges from 1 in 300 to 1 in 100. In children, the initial presentation of a rash can be mistaken for an infection, physicians should consider the possibility of a drug reaction in children that develop symptoms of a rash and fever during the first eight weeks of therapy.

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

- High initial doses of Lamotrigine and exceeding the recommended dose escalation of Lamotrigine therapy.
- Concomitant use of valproate, which increases the mean half-life of Lamotrigine nearly two fold.

All patients (adults and children) who develop a rash should be promptly evaluated and Lamotrigine should be withdrawn immediately unless the rash is clearly not drug related. Rash has also been reported as part of hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and Lamotrigine discontinued if an alternative aetiology cannot be established. As with other AED's, abrupt withdrawal of Lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine should be gradually decreased over a period of 2 weeks. When concomitant antiepileptic drugs (AED's) are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AED's) are added-on to Lamotrigine monotherapy consideration should be given to the effect this may have on Lamotrigine pharmacokinetics. During clinical experience with Lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis dysfunction and disseminated intravascular coagulation (DIC). The contribution of Lamotrigine to these events remains to be established. Lamotrigine is a weak inhibitor of dihydrofolate reductase hence there is a possibility of interference with folate metabolism during long-term therapy. However, during prolonged human dosing, Lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years. In single dose studies in subjects with end stage renal failure, plasma concentrations of Lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should be exercised in treating patients with renal failure.

Use in pregnancy and lactation

Fertility: Administration of Lamotrigine did not impair fertility in animal reproductive studies. There is no experience of the effect of Lamotrigine on human fertility. *Teratogenicity:* Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects. *Pregnancy:* There are insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus. *Lactation:* Preliminary data indicate that Lamotrigine passes into breast milk in concentrations usually of the order of 40-45% of the plasma concentration. In the small number of infants known to have been breastfed, the dose of Lamotrigine received was calculated to be approximately 0.06-0.75 mg/kg/24 hours, and no adverse experiences were reported.

Effects on Ability to Drive and Use Machines

Two volunteer studies have demonstrated that the effect of Lamotrigine on fine visual motor-coordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with Lamotrigine adverse events of neurological character such as dizziness and diplopia have been reported. As there is individual variation in response to all antiepileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.

Drug Interactions

Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbitone and primidone) enhance the metabolism of Lamotrigine and may increase dose requirements. Sodium valproate, which competes with Lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of Lamotrigine. There is no evidence that Lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolizing enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences. Although changes in the plasma concentrations of other antiepileptic drugs have been reported, controlled studies have shown no evidence that Lamotrigine affects the plasma concentrations of concomitant antiepileptic drugs. Evidence from in vitro studies indicates that Lamotrigine does not displace other antiepileptic drugs from protein binding sites. There have been reports of central nervous system events including headache, nausea, blurred vision, dizziness, diplopia and ataxia in patients taking carbamazepine following the introduction of Lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

In a study of 12 female volunteers, Lamotrigine did not affect plasma concentrations of ethinyloestradiol and levonorgestrel following the administration of the oral contraceptive pill. However, as with the introduction of other chronic therapy in patients taking oral contraceptives, any change in the menstrual bleeding pattern should be reported to the patient's physician.

SIDE EFFECTS

Adverse experiences reported during Lamotrigine monotherapy trials include headache, tiredness, rash, nausea, dizziness, drowsiness and insomnia. In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking Lamotrigine and in 5% of patients taking placebo. The skin rashes led to the withdrawal of Lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamotrigine. Rarely, serious potentially life threatening skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis (Lyell Syndrome) have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death. Other adverse experiences reported when Lamotrigine is added-on to standard antiepileptic drug regimens have included diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, headache, unsteadiness, tiredness, gastrointestinal disturbance (including vomiting), irritability/aggression, tremor, agitation, confusion and haematological abnormalities (including neutropenia, leucopenia and thrombocytopenia).

OVERDOSAGE

Ingestion of between 1.35 and 4 g Lamotrigine has been reported in a few patients. Clinical consequences were not severe, signs and symptoms included nystagmus, ataxia, dizziness, somnolence, headache and vomiting. A patient who ingested a dose calculated to be between 4 and 5 g Lamotrigine was admitted to hospital with coma lasting 8-12 hours followed by recovery over the next 2 to 3 days. A further patient who ingested 5.6 g Lamotrigine was found unconscious. Following treatment with activated charcoal for suspected intoxication the patient recovered after sleeping for 16 hours. In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

STORAGE

Store below 25°C.

PRESENTATIONS

Tablets:

AMOGINE 25: Lamotrigine 25 mg/tablet
AMOGINE 50: Lamotrigine 50 mg/tablet
AMOGINE 100: Lamotrigine 100 mg/tablet
AMOGINE 150: Lamotrigine 150 mg/tablet
AMOGINE 200: Lamotrigine 200 mg/tablet

Excipients: Lactose, Sodium starch glycolate, Microcrystalline cellulose, Povidone, Magnesium stearate, yellow iron oxide, FD&C yellow no 6 lake, FD&C blue lake.

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by:
HIKMA Pharmaceuticals, Amman-Jordan

HIKMA

Keep medicament out of the reach of children

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