

Lamotrigine and congenital malformations

SPC text agreed by the PhVWP 30May2006

Section 4.6 (pregnancy)

Risk related to antiepileptic drugs in general

Specialist advice should be given to women who are of childbearing potential. The need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. Sudden discontinuation of antiepileptic therapy should be avoided as this may lead to breakthrough seizures which could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptics compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects.

Multiple antiepileptic drug therapy is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to lamotrigine

Epidemiological studies involving in total approximately 2000 women exposed to lamotrigine monotherapy during pregnancy cannot exclude an increased risk for congenital malformations. One registry has reported an increased incidence of facial clefts. Other data sets have not confirmed this finding. Animal studies have shown developmental toxicity (see section 5.3).

If therapy with lamotrigine is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofetal damage by reducing folic acid levels. Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine plasma levels during pregnancy. Appropriate clinical management of pregnant women during lamotrigine therapy should be ensured.

Section 5.3 (preclinical safety data)

In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but reduced foetal weight and retarded skeletal ossification were observed, at exposure levels below or similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, the teratogenic potential of lamotrigine has not been characterised above clinical exposure.

In rats, enhanced foetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (day 15-20). These effects were observed at the expected clinical exposure.

Animal experiments did not reveal impairment of fertility by lamotrigine. Lamotrigine reduced foetal folic acid levels in rats. Folic acid deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.