

Draft Letter to MAHs for ACE inhibitors

To Responsible Pharmacist/ MAH contact
MAH
Address

Re : Product - Request to submit type II variation following PhVWP Recommendations on the use during the 1st trimester of pregnancy

Dear X,

Following review and discussion regarding the teratogenic potential of ACE inhibitors, the Pharmacovigilance Working Party (PhVWP) concluded at its meeting in October 2007 that the contra-indication of ACE inhibitors during the first trimester of pregnancy is not justified given the limited evidence related to a teratogenic risk.

Cooper's study published in the NEJM in June 2007 has identified a signal of increased risk of congenital malformations, particularly cardiac defects after exposure to ACE inhibitors during the first trimester of pregnancy. Since the role of confounding factors such as diabetes and hypertension cannot be accurately defined based on the available data, the teratogenic potential of ACE inhibitors is not demonstrated, even though data suggest that such exposure cannot be considered as safe and should be avoided. This conclusion is further supported by data from a couple of European based pregnancy registries not yet published as well as two other studies, published as abstracts:

- *A French study compared the outcome of 159 pregnancies with exposure to ACE inhibitors during the first trimester of pregnancy and 159 control pregnancies and did not show an increased risk of congenital malformation (RR=1.5; 95% CI 0.3- 6.5).*
- ENTIS data have included the analysis of the outcome of 452 prospectively collected pregnancies exposed to ACE inhibitors during the first trimester of pregnancy. A rate of birth defects of 3.1% was found which is not indicative of teratogenic effects for ACE inhibitors and that there is no pattern of defects over-presented.

Clinical practice shows that some women with severe hypertension and other risk factors such as diabetes or renal diseases benefit from continuing therapy with ACE Inhibitors until the beginning of pregnancy before switching to a suitable alternative treatment.

According to the draft "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling"(EMA/CHMP/203927/2005), the contra-indication in pregnancy must be mentioned in the SPC only when the risk to the pregnancy or the developing foetus/ unborn child significantly outweighs the potential benefit to the mother or the child.

Therefore, the contra-indication during the first trimester of pregnancy should be deleted from the Product Information of ACE inhibitors, when indicated.

In order to strengthen the current product information of ACE inhibitors related to pregnancy and to harmonise the product information across the class, the wording to be included in the sections 4.3 "contra-indication", 4.4 "Warning and precautions for use" and 4.6 "Pregnancy and lactation" of the SPC is as follows :

Section 4.3 Contraindication

Second and third trimester of pregnancy (see sections 4.4 and 4.6)

Section 4.4 Special warnings and precautions for use

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitors is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Section 4.6 Pregnancy and lactation

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitors therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3).

Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4)."

The above SPC changes should also be reflected in the patient information leaflets as follows :

Section 2 –

Contra-indication

Don't take (the product) if you are pregnant of 3 months or more.

Warning and precautions for use

This product is usually not recommended during the first trimester of pregnancy and the breastfeeding.

Use in pregnancy / breastfeeding

Before taking (the product), inform your physician if you are pregnant, if you think that you may be pregnant or if you plan to be pregnant. It is preferable not to use (the product) during the first trimester of pregnancy.

If you become pregnant during therapy with (the product), please inform and see your physician without delay. The product should not be used during the second and third trimester of pregnancy. Appropriate antihypertensive drug must usually replace (the product) before starting a pregnancy.

Please note that you are requested to submit a type II application within 2 months in order to implement these changes to the Product Information of [the product] according to the CHMP request.

The submission of supportive documents in this type II variation application is not necessary.