

## Draft Letter to MAHs for AIIRAs

To Responsible Pharmacist/ MAH contact  
MAH  
Address

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

Dear X,

Following review and discussion at the September 2007 PhVWP on the teratogenic potential of ACE inhibitors and Angiotensin II Receptor Antagonists (AIIRAs), the CHMP agreed during its October 2007 meeting to harmonise the product information of AIIRAs with regards to pregnancy and 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.

There are fewer data regarding the risks associated with first trimester exposure to AIIRAs than for ACE inhibitors. Nevertheless, there is no evidence that the risk is lower for AIIRAs, and the CHMP considers that any conclusions on ACE inhibitors are also valid for AIIRAs.

Clinical practice show that some women with severe hypertension and other risk factors such as diabetes or renal diseases benefit from continuing therapy with Angiotensin II Receptor Antagonists (AIIRAs), 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"(EMEA/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 AIIRAs, when indicated.

In order to strengthen the current product information of Angiotensin II Receptor Antagonists (AIIRAs), 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: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs 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 AIIRAs 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 AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs 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. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors( AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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 AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data').

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

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

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

“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].

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

**For CAP:** A 30-day timetable will be applied for the assessment of this application. Please refer to the EMEA Post-Authorisation Guidance for details on the presentation of this submission (<http://www.emea.europa.eu/htms/human/postguidance/list.htm>).

