

Hydrochlorothiazide (HCTZ) and use in lactation + consolidated wording for the SmPC and PL of ACE-inhibitors alone or in combination with HCTZ in pregnancy and lactation

Final SmPC and PL wording Agreed by PhVWP in June 2011

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ANNEX 1: SPC text/text in blue = new text

Substance and source of text	SPC wording in section 4.3	SPC wording in section 4.4	SPC wording in section 4.6	SPC wording in section 5.2
<p>Lisinopril, fosinopril, trandopril, moexipril, perindopril</p> <p>Spirapril, delapril</p>	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).</p>	<p><i>Pregnancy</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p>	
<p>Lisinopril, fosinopril, trandopril,</p>	<p>[Comment: No contraindication in Section 4.3 for</p>		<p><i>Lactation:</i> Because no information is available regarding the use of [Product]</p>	

moexipril, perindopril Spirapril, delapril	lactation.]		during breastfeeding, [Product] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.	
Fosinopril	[Comment: No contraindication in Section 4.3 for lactation.]		<i>Lactation:</i> Because only very limited information is available regarding the use of [Product] during breastfeeding, [Product] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.	
Ramipril	<i>Contraindication</i> 2 nd and 3 rd trimester of pregnancy (see sections 4.4 and 4.6)	<i>Pregnancy:</i> ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ 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 ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).	<i>Pregnancy:</i> TRITACE is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3). 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 inhibitor 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 inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) 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 ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).	
Ramipril	[Comment: No contraindication in		<i>Lactation:</i> Because insufficient information is	A single oral dose of ramipril

	Section 4.3 for lactation.]		available regarding the use of ramipril during breastfeeding (see section 5.2), ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant..	produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.
Benazepril	<i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).	<i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).	<i>Pregnancy</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimesters 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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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. Exposure to ACE inhibitor therapy 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 inhibitor 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 section 4.3 and 4.4).	
Benazepril	[Comment: No contraindication in Section 4.3 for lactation.]		<i>Lactation:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not	<i>Lactation:</i> In nine women given an oral dose of 20 mg of benazepril daily for 3 days (time postpartum not stated), peak milk levels of 0.9 µg/L of benazepril at 1 hour after the dose and 2 µg/L of its active

			<p>enough clinical experience.</p> <p>In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p>	<p>metabolite benazeprilat at 1.5 hours after the dose were detected.</p> <p>It is estimated that the breastfed infant would receive a daily dose less than 0.14% of the maternal weight-adjusted dose of benazepril.</p>
Captopril	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).</p>	<p><i>Pregnancy:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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).</p>	
Captopril	<p>[Comment: No contraindication in Section 4.3 for lactation.]</p>		<p><i>Lactation:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after</p>	<p><i>Lactation:</i> In the report of twelve women taking oral captopril 100 mg 3 times daily, the average peak milk level was 4.7µg/L and occurred 3.8 hours</p>

			<p>delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.</p> <p>In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p>	<p>after the dose.</p> <p>Based on these data, the maximum daily dosage that a nursing infant would receive is less than 0.002% of the maternal daily dosage.</p>
Enalapril	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).</p>	<p><i>Pregnancy:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p>	
Enalapril	<p>[Comment: No contraindication in Section 4.3 for lactation.]</p>		<p><i>Lactation:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and</p>	<p><i>Lactation:</i> After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak</p>

			<p>because there is not enough clinical experience. In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p>	<p>enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.</p>
Quinapril	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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</p>	<p><i>Pregnancy:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an</p>	

		should be started (see sections 4.3 and 4.6).	<p>established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p>	
Quinapril	[Comment: No contraindication in Section 4.3 for lactation.]		<p><i>Lactation:</i></p> <p>Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p>	<p><i>Lactation:</i></p> <p>After a single oral dose of 20 mg of quinapril in six breast-feeding women, the M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5 µg/L) at all time points. It is estimated that a breastfed infant would receive about 1.6% of the maternal weight-adjusted dosage of quinapril.</p>
Angiotensin II Receptor Antagonists (AIIRAs)	<i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).	<i>Pregnancy:</i> AIIRAs should not be initiated during pregnancy. Unless continued AIIRA 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	<p><i>Pregnancy:</i></p> <p>The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).</p> <p>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</p>	

		stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).	<p>Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.</p> <p>Exposure to AIIRA therapy 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 section 5.3.) Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.</p> <p>Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).</p>	
Angiotensin II Receptor Antagonists (AIIRAs)	[Contraindication for lactation to be deleted, if applicable]		<p><i>Lactation:</i></p> <p>Because no information is available regarding the use of [Product] during breastfeeding, [Product] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.</p>	
Valsartan	<i>In accordance with SPC wording for Angiotensin II Receptor Antagonists (AIIRAs) as published on CMD(h) website in Dec 08.</i>	<i>In accordance with SPC wording for Angiotensin II Receptor Antagonists (AIIRAs) as published on CMD(h) website in Dec 08.</i>	<i>In accordance with SPC wording for Angiotensin II Receptor Antagonists (AIIRAs) as published on CMD(h) website in Dec 08.</i>	
HCTZ	[Comment: No contraindication in Section 4.3 for pregnancy.]		<p><i>Pregnancy:</i></p> <p>There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.</p> <p>Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or</p>	

			<p>preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.</p> <p>Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
HCTZ	[Comment: No contraindication in Section 4.3 for lactation.]		<p><i>Lactation</i></p> <p>Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	
HCTZ in combination with valsartan	<p><i>Contraindication</i></p> <p>Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy wording is in accordance with SPC wording for Angiotensin II Receptor Antagonists (AIIRAs) as published on CMD(h) website in Dec 08.</i></p>	<p><i>Pregnancy wording is in accordance with SPC wording for Angiotensin II Receptor Antagonists (AIIRAs) as published on CMD(h) website in Dec 08. In addition the following text is included:</i></p> <p>Hydrochlorothiazide</p> <p>There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.</p> <p><i>Lactation</i></p> <p>No information is available regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of Diovan Comp during breast feeding is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.</p>	
HCTZ in combination with lisinopril, trandopril, moexipril, perindopril, spirapril, delapril	<p><i>Contraindication</i></p> <p>Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i></p> <p>ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive</p>	<p><i>Pregnancy</i></p> <p><i>ACE-inhibitors:</i></p> <p>The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</p> <p><i>Epidemiological evidence regarding</i></p>	

		<p>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).</p>	<p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p> <p><i>Hydrochlorothiazide:</i></p> <p>There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.</p> <p>Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.</p> <p>Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
HCTZ in combination	[Comment: No contraindication in		<i>Lactation ACE-inhibitors:</i>	

<p>with lisinopril,trandopril,moexipril,perindopril</p>	<p>Section 4.3 for lactation.]</p>		<p>Because no information is available regarding the use of [Product] during breastfeeding, [Product] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	
<p>HCTZ in combination with fosinopril</p>	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).</p>	<p><i>Pregnancy ACE-inhibitors:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p>	

			<p><i>Hydrochlorothiazide:</i> There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
HCTZ in combination with fosinopril	[Comment: No contraindication in Section 4.3 for lactation.]		<p><i>Lactation</i> <i>Fosinopril:</i> Because only very limited information is available regarding the use of [Product] during breastfeeding, [Product] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	
HCTZ in combination with ramipril	<i>Contraindication</i> 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6) <i>Lactation</i> (see section 4.6)	<i>Pregnancy:</i> ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an	<i>Pregnancy</i> TRITAZIDE is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3). 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 inhibitor therapy is considered essential, patients planning	

		<p>established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).</p>	<p>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 inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) 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 ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).</p> <p>Hydrochlorothiazide, in cases of prolonged exposure during the third trimester of pregnancy, may cause a foeto-placental ischaemia and risk of growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported in case of exposure near term. Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.</p>	
<p>HCTZ in combination with ramipril</p>	<p><i>Contraindication</i> Lactation (see section 4.6)</p>		<p><i>Lactation:</i> TRITAZIDE is contraindicated during breast-feeding. Ramipril and hydrochlorothiazide are excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of ramipril and hydrochlorothiazide are administered to breast-feeding women. Insufficient information is available regarding the use of ramipril during breast-feeding and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.</p> <p>Hydrochlorothiazide is excreted in human milk. Thiazides during breast-feeding by lactating mothers have been associated with a decrease or even suppression of lactation. Hypersensitivity to sulphonamide-</p>	

			<p>derived active substances, hypokalaemia and nuclear icterus might occur. Because of the potential for serious reactions in nursing infants from both active substances, a decision should be made whether to discontinue nursing or to discontinue therapy taking account of the importance of this therapy to the mother.</p>	
<p>HCTZ in combination with benazepril</p>	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).</p>	<p><i>Pregnancy</i> <i>ACE-inhibitors:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p> <p><i>Hydrochlorothiazide:</i> There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester</p>	

			<p>may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.</p> <p>Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.</p> <p>Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
HCTZ in combination with benazepril	[Comment: No contraindication in Section 4.3 for lactation.]		<p><i>Lactation Benazepril:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	<p><i>Lactation:</i> In nine women given an oral dose of 20 mg of benazepril daily for 3 days (time postpartum not stated), peak milk levels of 0.9 µg/L of benazepril at 1 hour after the dose and 2 µg/L of its active metabolite benazeprilat at 1.5 hours after the dose were detected. It is estimated that the breastfed infant would receive a daily dose less than 0.14% of the maternal weight-adjusted dose of benazepril.</p>
HCTZ in combination with captopril	<i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).	<i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE	<p><i>Pregnancy ACE-inhibitors:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</p> <p>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</p>	

		<p>inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).</p>	<p>inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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).</p> <p><i>Hydrochlorothiazide:</i> There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
<p>HCTZ in combination with captopril</p>	<p>[Comment: No contraindication in Section 4.3 for lactation.]</p>		<p><i>Lactation Captopril:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not</p>	<p><i>Lactation:</i> In the report of twelve women taking oral captopril 100 mg 3 times daily, the average peak milk level was 4.7µg/L and</p>

			<p>recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	<p>occurred 3.8 hours after the dose. Based on these data, the maximum daily dosage that a nursing infant would receive is less than 0.002% of the maternal daily dosage.</p>
<p>HCTZ in combination with enalapril</p>	<p><i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).</p>	<p><i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).</p>	<p><i>Pregnancy ACE-inhibitors:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</p> <p>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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.</p> <p>When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>Exposure to ACE inhibitor therapy 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 inhibitor 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</p>	

			<p>observed for hypotension (see sections 4.3 and 4.4).</p> <p><i>Hydrochlorothiazide:</i> There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
HCTZ in combination with enalapril	[Comment: No contraindication in Section 4.3 for lactation.]		<p><i>Lactation Enalapril:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	<p><i>Lactation:</i> After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of</p>

				0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.
HCTZ in combination with quinapril	<i>Contraindication</i> Second and third trimesters of pregnancy (see sections 4.4 and 4.6).	<i>Pregnancy:</i> ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).	<i>Pregnancy ACE-inhibitors:</i> The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated 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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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. Exposure to ACE inhibitor therapy 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 inhibitor 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	

			<p>sections 4.3 and 4.4).</p> <p><i>Hydrochlorothiazide:</i> There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
HCTZ in combination with quinapril	[Comment: No contraindication in Section 4.3 for lactation.]		<p><i>Lactation</i> <i>Quinapril:</i> Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of [Product] in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of [Product] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	<p><i>Lactation:</i> After a single oral dose of 20 mg of quinapril in six breast-feeding women, the M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5 µg/L) at all time points. It is estimated that a breastfed infant would receive about 1.6% of the maternal weight-adjusted dosage of quinapril.</p>
HCTZ in combination with angiotensin	<i>Contraindication</i> Second and third trimesters of pregnancy (see	<i>Pregnancy:</i> AIIRAs should not be initiated during pregnancy. Unless	<i>Pregnancy</i> <i>Angiotensin II Receptor Antagonists (AIIRAs):</i> The use of AIIRAs is not	

<p>II Receptor Antagonists (AIIRAs)</p>	<p>sections 4.4 and 4.6).</p>	<p>continued AIIRA 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).</p>	<p>recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).</p> <p>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 AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.</p> <p>Exposure to AIIRA therapy 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 section 5.3.) Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.</p> <p>Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).</p> <p><i>Hydrochlorothiazide:</i> There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and</p>	
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			<p>placental hypoperfusion, without a beneficial effect on the course of the disease.</p> <p>Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.</p>	
<p>HCTZ in combination with angiotensin II Receptor Antagonists (AIIRAs)</p>	<p>[Contraindication for lactation to be deleted, if applicable]</p>		<p><i>Lactation</i> <i>Angiotensin II Receptor Antagonists (AIIRAs):</i> Because no information is available regarding the use of [Product] during breastfeeding, [Product] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.</p> <p><i>Hydrochlorothiazide:</i> Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.</p>	

ANNEX 2: PL text/text in blue = new text

Substance and source of text	PL wording
<p>Lisinopril, fosinopril, trandopril, moexipril, perindopril</p> <p>Spirapril, delapril</p>	<p>Before you take [Product]</p> <p>Do not take [Product] If you are more than 3 months pregnant. (It is also better to avoid [Product] in early pregnancy – see pregnancy section.)</p> <p>Take special care with [Product] You must tell your doctor if you think you are (or might become) pregnant. [Product] is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding</p> <p>Pregnancy You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking [Product] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Product]. [Product] is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.</p> <p>Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. [Product] is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.</p>
<p>Ramipril</p>	<p>Before you take [Product]</p> <p>Do not take [Product] During the last 6 months of pregnancy (see section below on “Pregnancy and breast-feeding”)</p> <p>Take special care with [Product] You must tell your doctor if you think that you are (or might become) pregnant. TRITACE is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy (see section below on “Pregnancy and breast-feeding”).</p> <p>Pregnancy and breast feeding You must tell your doctor if you think that you are (or might become) pregnant You should not take TRITACE in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby. If you become pregnant while on TRITACE, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. You should not take TRITACE if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.</p>
<p>Benazepril, captopril, enalapril, quinapril</p>	<p>Before you take [Product]</p> <p>Do not take [Product] If you are more than 3 months pregnant. (It is also better to avoid [Product] in early pregnancy – see pregnancy section.)</p> <p>Take special care with [Product] You must tell your doctor if you think you are (or might become) pregnant. [Product] is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding</p> <p>Pregnancy You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking [Product] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Product]. [Product] is not recommended in early pregnancy, and must not be taken when more than 3</p>

	<p>months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.</p> <p>Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast-feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking [Product]. In the case of an older baby your doctor should advise you on the benefits and risks of taking [Product] whilst breast-feeding, compared with other treatments.</p>
Angiotensin II Receptor Antagonists (AIIAs)	<p>Do not take [Product] If you are more than 3 months pregnant. (It is also better to avoid [Product] in early pregnancy – see pregnancy section.) [Contraindication for lactation to be deleted, if applicable]</p> <p>Take special care with [Product] You must tell your doctor if you think you are (or might become) pregnant. [Product] is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding Pregnancy You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking [Product] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Product]. [Product] is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. [Product] is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.</p>
Valsartan	<p>Do not take Diovan If you are more than 3 months pregnant. (It is also better to avoid Diovan in early pregnancy – see pregnancy section.)</p> <p>Take special care with Diovan You must tell your doctor if you think you are (or might become) pregnant. Diovan is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding Pregnancy You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Diovan before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Diovan. Diovan is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. Diovan is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.</p>
HCTZ	<p>Pregnancy You must tell your doctor if you are pregnant or if you think that you are. Usually, your doctor will advise you to take another medicine instead of [product], as [product] is not recommended during pregnancy. This is because [product] crosses the placenta and its use after the third month of pregnancy may cause potentially harmful foetal and neonatal effects.</p>
HCTZ	<p>Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. [Product] is not recommended for mothers who are breast-feeding.”</p>
HCTZ in combination with valsartan	<p>Do not take Diovan Comp: If you are more than 3 months pregnant. (It is also better to avoid Diovan Comp in early pregnancy – see pregnancy section.)</p>

	<p>Take special care with Diovan You must tell your doctor if you think you are (<u>or might become</u>) pregnant. Diovan Comp is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding Pregnancy You must tell your doctor if you think you are (<u>or might become</u>) pregnant. Your doctor will normally advise you to stop taking Diovan Comp before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Diovan Comp. Diovan Comp is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. Diovan Comp is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.</p>
<p>HCTZ in combination with lisinopril, fosinopril, trandopril, moexipril, perindopril, spirapril, delapril</p>	<p>Before you take [Product] Do not take [Product] If you are more than 3 months pregnant. (It is also better to avoid [Product] in early pregnancy – see pregnancy section.)</p> <p>Take special care with [Product] You must tell your doctor if you think you are (<u>or might become</u>) pregnant. [Product] is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding Pregnancy You must tell your doctor if you think you are (<u>or might become</u>) pregnant. Your doctor will normally advise you to stop taking [Product] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Product]. [Product] is not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. [Product] is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.</p>
<p>HCTZ in combination with ramipril</p>	<p>Before you take [Product] Do not take [Product] During the last 6 months of pregnancy (see section below on “Pregnancy and breast-feeding”)</p> <p>Take special care with [Product] You must tell your doctor if you think that you are (or might become) pregnant. TRITAZIDE is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy (see section below on “Pregnancy and breast-feeding”).</p> <p>Pregnancy and breast feeding You must tell your doctor if you think that you are (or might become) pregnant You should not take TRITAZIDE in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby. If you become pregnant while on TRITAZIDE, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. You should not take TRITAZIDE if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.</p>
<p>Benazepril, captopril, enalapril, quinapril</p>	<p>Before you take [Product] Do not take [Product] If you are more than 3 months pregnant. (It is also better to avoid [Product] in early pregnancy –</p>

	<p>see pregnancy section.)</p> <p>Take special care with [Product] You must tell your doctor if you think you are (or might become) pregnant. [Product] is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding</p> <p>Pregnancy You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking [Product] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Product]. [Product] is not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.</p> <p>Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. [Product] is not recommended for mothers who are breast-feeding.</p>
<p>HCTZ in combination with angiotensin II Receptor Antagonists (AIIRAs)</p>	<p>Do not take [Product] If you are more than 3 months pregnant. (It is also better to avoid [Product] in early pregnancy – see pregnancy section.) [Contraindication for lactation to be deleted, if applicable]</p> <p>Take special care with [Product] You must tell your doctor if you think you are (or might become) pregnant. [Product] is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).</p> <p>Pregnancy and breast feeding</p> <p>Pregnancy You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking [Product] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Product]. [Product] is not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.</p> <p>Breastfeeding Tell your doctor if you are breast-feeding or about to start breast-feeding. [Product] is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.</p>