

Annex II

**Amendments to relevant sections of the summary of product characteristics
and package leaflet**

For products containing the angiotensin-converting enzyme inhibitors (ACE-inhibitors) benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril and zofenopril, the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

For all ACE-inhibitors with wording in section 4.1 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added: "*(see sections 4.3, 4.4, 4.5 and 5.1)*".

Section 4.2 - Posology and method of administration

For all ACE-inhibitors with wording in section 4.2 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added: "*(see sections 4.3, 4.4, 4.5 and 5.1)*".

Section 4.3 – Contraindication

The following contraindication should be added to this section:

"The concomitant use of [Product name] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1)."

Section 4.4 - Special warnings and precautions for use

The following wording should be incorporated in this section:

"Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy."

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The following wording should be added to this section:

"Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated

with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1)."

Section 5.1 – Pharmacodynamic properties

The following wording should be added to this section:

"Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group."

II. Package leaflet

The following wording should be included in the specified sections:

Section 2. What you need to know before you <take> <use> X

Do not <take> <use> X <:>

- *"if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren"*

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

- *"if you are taking any of the following medicines used to treat high blood pressure:*

- an angiotensin II receptor blocker (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems.
- aliskiren"

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not <take> <use> X"

Other medicines and X

Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.

"Your doctor may need to change your dose and/or to take other precautions:

If you are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings "Do not <take> <use> X" and "Warnings and precautions")"

For products containing the angiotensin II receptor blockers azilsartan, eprosartan, irbesartan, losartan, olmesartan and telmisartan, the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

For angiotensin II receptor blockers with wording in section 4.1 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added:
“(see sections 4.3, 4.4, 4.5 and 5.1)”.

Section 4.2 - Posology and method of administration

For angiotensin II receptor blockers with wording in section 4.2 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added:
“(see sections 4.3, 4.4, 4.5 and 5.1)”.

Section 4.3 – Contraindication

The following contraindication should be added to this section:

“The concomitant use of [Product name] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).”

Section 4.4 - Special warnings and precautions for use

The following wording should be incorporated in this section:

“Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.”

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The following wording should be added to this section:

“Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal

function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1)."

Section 5.1 – Pharmacodynamic properties

The following wording should be added to this section (for telmisartan-containing products that already have an extensive wording on ONTARGET in section 5.1, the following wording should be added in addition to the existing text, which should be maintained):

"Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group."

II. Package leaflet

The following wording should be included in the specified sections:

PL Section 2. What you need to know before you <take> <use> X

Do not <take> <use> X <:>

- *"if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren"*

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

- *"if you are taking any of the following medicines used to treat high blood pressure:*

- an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
- aliskiren

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not <take> <use> X"

Other medicines and X

Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.

"Your doctor may need to change your dose and/or to take other precautions:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not <take> <use> X" and "Warnings and precautions")"

For products containing candesartan, the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

For candesartan-containing products with wording in section 4.1 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added: "*(see sections 4.3, 4.4, 4.5 and 5.1)*".

In addition, the existing heart failure indication should be revised as follows:

"The treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction \leq 40%) when ACE-inhibitors are not tolerated or as add-on therapy to ACE-inhibitors in patients with symptomatic heart failure, despite optimal therapy, when mineralocorticoid receptor antagonists are not tolerated (see sections 4.2, 4.4, 4.5 and 5.1)".

Section 4.2 - Posology and method of administration

The following cross-reference should be added to the "Posology in Hypertension" section: "*(see sections 4.3, 4.4, 4.5 and 5.1)*".

The following wording should be added in the "Posology in Heart Failure" section:

"[Product name] can be administered with other heart failure treatment, including ACE-inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products. [Product name] may be co-administered with an ACE-inhibitor in patients with symptomatic heart failure despite optimal standard heart failure therapy when mineralocorticoid receptor antagonists are not tolerated. The combination of an ACE-inhibitor, a potassium-sparing diuretic and [Product name] is not recommended and should be considered only after careful evaluation of the potential benefits and risks (see sections 4.4, 4.8 and 5.1)."

Section 4.3 – Contraindication

The following contraindication should be added to this section:

"The concomitant use of [Product name] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1)."

Section 4.4 - Special warnings and precautions for use

The following wording should be incorporated in this section:

"Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy."

The following wording should be incorporated in the "Heart failure" section:

"Concomitant therapy with an ACE-inhibitor in heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when [Product name] is used in combination with an ACE-inhibitor. Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and candesartan is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy."

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The following wording should be added to this section:

"Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1)."

Section 5.1 – Pharmacodynamic properties

The following wording should be added to this section:

"Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as

compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group."

II. Package leaflet

The following wording should be included in the specified sections:

Section 1. What X is and what it is used for

"X can be used to treat adult heart failure patients with reduced heart muscle function when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used or in addition to ACE-inhibitors when symptoms persist despite treatment and mineralocorticoid receptor antagonists (MRA) cannot be used. (ACE-inhibitors and MRAs are medicines used to treat heart failure)."

Section 2. What you need to know before you <take> <use> X

Do not <take> <use> X <:>

- "if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren"

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

- "if you are taking any of the following medicines used to treat high blood pressure:
 - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
 - aliskiren
- if you are taking an ACE-inhibitor together with a medicine which belongs to the class of medicines known as mineralocorticoid receptors antagonists (MRA). These medicines are for the treatment of heart failure (see "Other medicines and X")."

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not <take> <use> X"

Other medicines and X

Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.

"Your doctor may need to change your dose and/or to take other precautions:

- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not <take> <use> X" and "Warnings and precautions")

- If you are being treated with an ACE-inhibitor together with certain other medicines to treat your heart failure, which are known as mineralocorticoid receptors antagonists (MRA) (for example spironolactone, eplerenone)."

For products containing valsartan, the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

For valsartan-containing products with wording in section 4.1 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added: "(see sections 4.3, 4.4, 4.5 and 5.1)".

In addition, for products authorised in the treatment of heart failure, the existing heart failure indication should be revised as follows:

"Heart Failure

Treatment of adult patients with symptomatic heart failure when ACE-inhibitors are not tolerated or in beta-blocker intolerant patients as add-on therapy to ACE-inhibitors when mineralocorticoid receptor antagonists cannot be used (see sections 4.2, 4.4, 4.5 and 5.1)."

Section 4.2 - Posology and method of administration

For valsartan-containing products with wording in section 4.2 stating that they can be used alone or in combination with other antihypertensive agents, the following cross-reference should be added: "(see sections 4.3, 4.4, 4.5 and 5.1)".

In addition, for products authorised in the treatment of heart failure, the following wording should be added in the "Heart failure" section:

Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE-inhibitor, valsartan and a beta blocker or a potassium-sparing diuretic is not recommended (see sections 4.4 and 5.1). Evaluation of patients with heart failure should always include assessment of renal function."

Section 4.3 – Contraindication

The following contraindication should be added to this section:

"The concomitant use of [Product name] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment ($GFR < 60 \text{ ml/min/1.73 m}^2$) (see sections 4.5 and 5.1)."

Section 4.4 - Special warnings and precautions for use

The following wording should be incorporated in this section:

"Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy."

In addition, for products authorised in the treatment of heart failure, the following wording should be incorporated in the "Heart failure" section:

"Heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when [Product name] is used in combination with an ACE-inhibitor. In patients with heart failure, the triple combination of an ACE-inhibitor, a beta blocker and [Product name] has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended. Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and valsartan is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).

Use of [Product name] in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone-system (e.g. patients with severe congestive heart failure), treatment with ACE-inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II receptor blocker, it cannot be excluded that the use of [Product name] may be associated with impairment of the renal function.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy."

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The following wording should be added to this section:

"Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal

function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1)."

Section 5.1 – Pharmacodynamic properties

The following wording should be added to this section:

"Two large randomised, controlled trials (ONTARGET (ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group."

II. Package leaflet

The following wording should be included as applicable in the specified sections:

Section 1. What X is and what it is used for

"X can be used to treat symptomatic heart failure in adult patients. X is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE-inhibitors when other medications to treat heart failure cannot be used."

Section 2. What you need to know before you <take> <use> X

Do not <take> <use> X <:>

- *"if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren"*

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

- *“if you are taking any of the following medicines used to treat high blood pressure:
- an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
- aliskiren*
- *- if you are being treated with an ACE-inhibitor together with certain other medicines to treat your heart failure, which are known as mineralocorticoid receptors antagonists (MRA) (for example spironolactone, eplerenone) or betablockers (for example metoprolol).*

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not <take> <use> X”

Other medicines and X

Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.

“Your doctor may need to change your dose and/or to take other precautions:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not <take> <use> X” and “Warnings and precautions”)

If you are being treated with an ACE-inhibitor together with certain other medicines to treat your heart failure, which are known as mineralocorticoid receptors antagonists (MRA) (for example spironolactone, eplerenone) or betablockers (for example metoprolol).”

For products containing aliskiren, the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below

I. Summary of Product Characteristics

Section 4.3 – Contraindication

The following contraindication should be reflected in this section:

"The concomitant use of [Product name] with an ACE-inhibitor or an angiotensin II receptor blocker is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.4, 4.5 and 5.1)."

Section 4.4 - Special warnings and precautions for use

The following wording should be reflected in this section:

*"Dual blockade of the renin-angiotensin-aldosterone-system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia and decreased renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the RAAS by combining aliskiren with an ACE-inhibitor or an angiotensin II receptor blocker is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes, and blood pressure."*

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The following wording should be added to this section:

"Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, stroke, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1)."

II. Package leaflet

The following wording should be included in the specified sections:

Section 2. What you need to know before you <take> <use> X

Do not <take> <use> X <:>

- *"if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
- an ACE-inhibitor such as enalapril, lisinopril, ramipril.
or
- an angiotensin II receptor blocker such as valsartan, telmisartan, irbesartan."*

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

- *“if you are taking either of the following classes of medicines used to treat high blood pressure:
- an ACE-inhibitor such as enalapril, lisinopril, ramipril.
or
- an angiotensin II receptor blocker such as valsartan, telmisartan, irbesartan.*

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not <take> <use> X”

Other medicines and X

“If you are taking an angiotensin II receptor blocker (ARB) or an ACE-inhibitor, (see also information under the headings “Do not <take> <use> X” and “Warnings and precautions”)”