The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 February 2013

RASILEZ 150 mg, film-coated tablets
B/30 (CIP: 399 008-4)

RASILEZ 300 mg, film-coated tablets
B/30 (CIP: 399 009-0)

Applicant: NOVARTIS PHARMA SAS

aliskiren
ATC Code: C09XA02 (renin-inhibitor)

List I

Date of Marketing Authorisation: 22 August 2007 (centralised procedure)

Reason for review: Re-assessment of the Actual Benefit and the Improvement in Actual Benefit, initiated by the Transparency Committee (pursuant to Article R-163-21 of the French Social Security Code).
1 CONTEXT OF THE ASSESSMENT

The ALTITUDE trial is the first study that has evaluated the benefit of the proprietary medicinal product RASILEZ (aliskiren) in terms of morbidity and mortality. This study, carried out on patients with type II diabetes and renal impairment was stopped prematurely due to:

- an excessive number of cardiovascular events (in particular non-fatal stroke and cardiovascular-related deaths) and a higher incidence of renal complications, hyperkalaemia and hypotension observed in the aliskiren group in combination with conventional treatment including an ACEI or an ARB II compared with the placebo group.
- the non achievement of a fixed study objective; from the beginning there was no likelihood of demonstrating the hypothesis of superiority compared with placebo.

Considering recent clinical data and in particular the premature stopping of the ALTITUDE study, the Transparency Committee would like to re-assess the Actual Benefit (AB) of the proprietary medicinal product RASILEZ (aliskiren).

A re-assessment of the benefit/risk relationship for aliskiren has, however, been carried out by EMA within the framework of Article 20 of regulation (EC) no. 726/2004. This was instigated by the European Commission following the information sent by the applicant regarding the premature stopping of the ALTITUDE study and a favourable opinion was given by EMA on 21 February 2012, but with certain restrictions in place (see Appendix 1).

Following the re-assessment of the benefit/risk relationship for aliskiren by EMA, changes were made to the SPC (EC decision of 20 April 2012). These amendments included changes to the contraindications to the concomitant use of aliskiren with ARB IIs or ACEIs in patients with diabetes or renal impairment and special warnings and precautions for use in other patients.

These are highlighted in bold below.

It should be noted that two other morbidity/mortality studies are currently in progress, on patients who are either hypertensive or not; one for acute heart failure and the second for chronic heart failure.
2 CHARACTERISTICS OF THE MEDICINAL PRODUCT

2.1. Active ingredient
Aliskiren

2.2. Therapeutic indications
"Treatment of essential hypertension (EHT)."

2.3. Dosage
"The recommended dose of RASILEZ is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily. The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with 150 mg once daily.

RASILEZ may be used alone or in combination with other antihypertensive agents with the exception of use in combination with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m²).

RASILEZ should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with RASILEZ.

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment. RASILEZ is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m²). Concomitant use of RASILEZ with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m²).

Hepatic impairment: No adjustment of the initial dose is required for patients with mild to severe hepatic impairment.

Elderly patients (aged 65 years and over): The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Children and adolescents (under 18 years)
RASILEZ is not recommended for use in children and adolescents below 18 years due to the absence of safety and efficacy data (see section 5.2 of SCP)."

2.4. Contraindications
"• Hypersensitivity to the active substance or to any of the excipients.
• History of angioedema with aliskiren.
• Hereditary or idiopathic angioedema.
• Second and third trimesters of pregnancy.
• The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-gp inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated.
• The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²)."

2.5. Special warnings and precautions for use
Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV).

In the event of severe and persistent diarrhoea, RASILEZ therapy should be stopped.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS) Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²).

Angioedema As with other medicinal products acting on the renin-angiotensin system, angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicines that can cause angioedema, including RAAS inhibitors (angiotensin converting enzyme inhibitors or angiotensin receptor blockers).

Patients with a history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren. Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment especially at the beginning of the treatment.

If angioedema occurs, RASILEZ should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Sodium and/or volume depleted patients In patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with RASILEZ. This depletion should be corrected prior to administration of RASILEZ, or the treatment should start under close medical supervision.

Renal impairment In clinical studies RASILEZ has not been investigated in hypertensive patients with severe renal impairment (serum creatinine ≥ 150 µmol/l or 1.70 mg/dl in women and ≥ 177 µmol/l or 2.00 mg/dl in men and/or estimated GFR < 30 ml/min/1.73 m²), history of dialysis, nephrotic syndrome or renovascular hypertension. **RASILEZ is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m²).**

As for other medicinal products acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. **The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m²).** Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.
Increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

Renal artery stenosis
No controlled clinical data are available on the use of RASILEZ in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore, caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Moderate P-gp inhibitors
Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. Therefore, caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil."
3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2012)
C : Cardiovascular system
C09 : Agents acting on the renin-angiotensin system
C09X : Other agents acting on the renin-angiotensin system
C09XA: Renin-inhibitors
C09XA02: aliskiren

3.2. Medicines in the same therapeutic category
There are no medicines in the same therapeutic category.

3.3. Medicines with a similar therapeutic aim
Other products indicated in the treatment of essential arterial hypertension:
- categories of medicinal products that have demonstrated a reduction in cardiovascular morbidity and mortality are: beta-blockers, diuretics, calcium inhibitors, angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB II).
- categories of medicinal products that have not demonstrated a benefit in mortality are: alpha-blockers and central antihypertensives.

4 REMINDER OF THE COMMITTEE’S OPINIONS AND CONDITIONS OF INCLUSION

Committee Opinion of 6 February 2008 (Inclusion)

AB:
“Essential arterial hypertension, due to its complications, can be life-threatening. This medicinal product is intended as a preventive therapy. The efficacy / adverse effects ratio, assessed on the reduction in blood pressure readings, is high. Alternative medicinal products exist. The therapeutic need is covered by other antihypertensives (thiazide diuretics, beta-blockers, calcium inhibitors, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers). In the absence of a demonstration in the reduction of morbidity and mortality, RASILEZ should, in fact, be considered as a second-line therapy. The actual benefit of this medicinal product is substantial.”

IAB:
“RASILEZ does not provide an improvement in actual benefit (IAB V) within the scope of a medicinal treatment for essential arterial hypertension. It is a useful additional treatment method.”

5 PRESCRIPTION INFORMATION

According to DOREMA data (IMS-EPPM, moving annual total August 2012), RASILEZ has been prescribed 547,000 times (284,000 prescriptions for RASILEZ 300 mg and 263,000 prescriptions for RASILEZ 150 mg). RASILEZ is mainly prescribed for arterial hypertension (91% to 94.6% of prescriptions, depending on the dosage).
In response to the request to re-assess the actual benefit of the proprietary medicinal product RASILEZ (aliskiren) by the Transparency Committee, the applicant has submitted a dossier including a literature review and study reports.

Those to be considered:
- studies where the aim was to determine the efficacy of aliskiren in terms of morbidity and mortality in a population of diabetic patients with renal impairment: ALTITUDE study\(^1\)
- studies and meta-analyses where the aim was to determine the efficacy of aliskiren with regards to interim or alternative endpoints in hypertensive patients (in accordance with the Marketing Authorisation indication): ALLAY\(^2\), AGELESS\(^3\), Gao\(^4\), ATLAAS\(^5\).
- meta-analyses that specifically investigated the safety of aliskiren in combination with another renin-angiotensin-aldosterone (RAS) inhibitor in hypertensive patients: Harel\(^6\).
- periodic pharmacovigilance reports (PSUR 1 to 7) covering the period from 05/03/2007 to 30/09/2011.

Those not considered in this opinion:
- studies carried out on non-hypertensive patients or controlled with hypertensive treatment on inclusion: ALOFT\(^7\), AVANT-GARDE\(^8\), ASPIRE\(^9\), studies
- studies with an invalid methodology: Chrysant 2010\(^10\) (non-comparative study), the post-hoc analysis of the Schmieder study\(^11\) and the pooled analysis of the White studies\(^12\).
- unpublished studies: the American (CSPV100AUS02) phase IV study, the final report from which is not available,
- clinical studies carried out with interim endpoints with no valid clinical consequences, such as inflammation markers: Krone\(^13\).
- clinical studies with the aim of evaluating the efficacy of the addition of another antihypertensive to aliskiren compared with aliskiren alone: Black\(^14\), study CSPP100A2410 (unpublished),
- studies that were not in accordance with current guidelines: ACCELERATE\(^15\) (study of the benefit of the combination aliskiren/amlopidine as a first-line treatment),

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\(^1\) Parving HH et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. NEJM online, November 3, 2012.
\(^2\) Solomon SD et al. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. Circulation 2009; 119:530-537.
\(^3\) Duprez DA et al. Aliskiren for Geriatric Lowering Of Systolic Hypertension: a randomized controlled trial. Journal of Human Hypertension 2010: 600–608.
- studies that evaluated the impact of forgetting to take aliskiren and the relationship between the time taken and efficacy: studies 2406, 2408, 2351, 2110 and 2405.

Studies already submitted and examined in the previous Transparency Committee Opinion will not be re-examined in this Opinion (for the results, refer to the Opinion of 6 February 2008); these are the Anderson 2008\(^\text{16}\) and Schmieder\(^\text{17}\) studies and studies 2302, 2305, 2304, 2301 and 2308.

Finally, the applicant has stated that there are two morbidity and mortality studies currently in progress, the ATMOSPHERE and ASTRONAUT studies.

### 6.1. Efficacy

#### 6.1.1. Morbidity and mortality study: ALTITUDE study

This is a study that aimed to determine the efficacy of aliskiren in combination with a conventional treatment, including in particular a RAS inhibitor, in terms of morbidity and mortality.

It was carried out on patients with type II diabetes and renal impairment. This study was stopped prematurely (on 14 December 2011) due to an increase in cardiovascular events (in particular an excess of non-fatal stroke) and a higher incidence of renal complications, hyperkalaemia and hypotension observed in the aliskiren group, combined with the conventional treatment including an ACEI or an ARB II, compared with the placebo group.

**Aim:**

The aim of this study was to demonstrate the superiority of aliskiren (n=4,283) versus placebo (n=4,296) in terms of the prevention of major cardiovascular and renal events (cardiovascular-related deaths, sudden death following resuscitation, myocardial infarction (MI) and non-fatal stroke, hospitalisation due to heart failure, terminal renal failure or renal-related death and persistent doubling of serum creatinine levels for at least one month), in patients with type 2 diabetes and a renal disorder taking multi-agent antihypertensive treatments including one RAS inhibitor.

**Method:**

A randomised, placebo controlled, double-blind comparative study of aliskiren 300 mg/day added to a conventional treatment, including an ACEI or an ARB II, which included 8,606 patients with type 2 diabetes and a renal disorder who were monitored over a mean duration of 32 months.

According to the interim study report sent by the applicant for the assessment of the medicinal product on 2 August 2012, on 31 January 2012, out of a total of 8,606 patients included, 1,434 events had been observed (88.5% of the events initially expected in the protocol).


Inclusion criteria: Patients 35 years or older with:
- type 2 diabetes receiving treatment or diagnosed (blood sugar level ≥ 7 mmol/l),
- and at least one of the following characteristics:
  - persistent macroalbuminuria defined as the urine albumin/creatinine ratio ≥ 200 mg/g and eGFR\(^{18}\) ≥ 30 ml/min/1.73 m\(^2\),
  - a persistent microalbuminuria defined as albumin/creatinine ratio of between 20 mg/g and 200 mg/g and a 30 ≤ eGFR < 60 ml/min/1.73 m\(^2\),
  - a history of cardiovascular disease (MI, stroke, heart failure, coronary disease - percutaneous coronary intervention / coronary bypass / stenosis ≥ 50% of at least one major pericardial artery) and 30 ≤ eGFR < 60 ml/min/1.73 m\(^2\).

Primary efficacy endpoint: occurrence of the first event from the following events (combined endpoint): cardiovascular-related death, sudden death following resuscitation, MI or non-fatal stroke, hospitalisation due to heart failure, terminal renal failure or renal-related death and persistent doubling of serum creatinine for at least one month.

RESULTS: on an intention to treat basis

This study stopped prematurely on 14 December 2011. According to the interim study report sent by the applicant for the assessment of the medicinal product on 2 August 2012, on 31 January 2012, 1,434 events had been observed, including 1,025 that were cardiovascular related.

This study was stopped at the second interim analysis, due to an increase in the aliskiren group:
- in the number of events included in the primary combined endpoint (cardiovascular-related death, sudden death following resuscitation, MI and non-fatal stroke, hospitalisation due to heart failure, terminal renal failure or renal-related death, persistent doubling of serum creatinine for at least one month): 748 patients (17.5%) in the aliskiren group versus 686 (16%) in the placebo group: HR 1.107 [0.996; 1.231], NS.
- an excessive number of strokes (secondary endpoint) observed in the aliskiren group: 144 patients (13.4%) in the aliskiren group and 113 patients (12.6%) in the placebo group, HR 1.29 [1.01; 1.65], p=0.043,
- an excessive number of adverse effects observed in the aliskiren group: hyperkalaemia, hypotension and renal impairment.

Given this data, contraindications and special warnings for use regarding interactions with other medicinal products have been included in the Marketing Authorisation for RASILEZ:
- Contraindication: the concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (Glomerular Filtration Rate GFR< 60 ml/min/1.73 m\(^2\)),
- Interaction with other medicinal products: the combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR< 60 ml/min/1.73 m\(^2\)) and is not recommended in other patients.

The final results were published on 3 November 2012 (Parving et al\(^1\)), after a median follow-up period of 32.9 months; all patients treated with RASILEZ had discontinued their treatment by the set date limit of 6 January 2012. The results were as follows:
- The number of events included in the combined primary endpoint observed was: 783 patients (18.3%) in the aliskiren group and 732 (17.1%) in the placebo group: HR 1.08 [0.98; 1.20], NS.
- Stroke (secondary endpoint) was observed in 147 patients (3.4%) in the aliskiren group and 122 patients (2.8%) in the placebo group, HR 1.22 [0.96; 1.55], NS.

\(^{18}\)Glomerular filtration rate
- Resuscitated cardiac arrests (secondary endpoint) were observed in 19 patients (0.4%) in the aliskiren group and 8 patients (0.2%) in the placebo group, HR 2.40 [1.05; 5.48], p=0.04.

6.1.2. Study of the interim endpoints: ALLAY study:

This randomised, double-blind study compared the efficacy in terms of the impact on the reduction in ventricular mass for aliskiren 300 mg with that of losartan 100 mg alone and the combination of them both, in 465 hypertensive (BP > 140/90 mmHg), overweight (BMI > 25 kg/m$^2$) patients with left ventricular hypertrophy. After 9 months of treatment, the mass of the left ventricle (primary efficacy endpoint) was significantly reduced in all treatment groups compared with on inclusion (-4.9 g/m$^2$ (5.4%) in the aliskiren group, -4.8 g/m$^2$ (4.7%) in the losartan group and -5.8 g/m$^2$ (6.4%) in the aliskiren + losartan group, p<0.001), however no significant difference was highlighted between the groups.

In conclusion, the addition of aliskiren to losartan does not provide an additional improvement in terms of the reduction of left ventricular mass.

6.1.3. Studies and meta-analysis of the reduction in blood pressure

As monotherapy:

The randomised, double-blind AGELESS study (Duprez 2010) compared the efficacy of aliskiren 150-300 mg/day with ramipril 5-10 mg/day, in 901 hypertensive patients (systolic blood pressure (SBP) > 140 mmHg) aged over 65 years. The majority of patients included were overweight (BMI > 25 kg/m$^2$), 40% of them were obese, 20% had diabetes and 32.5% were over 75 years. In this study, the efficacy was evaluated in terms of the reduction in SBP.

The non-inferiority of treatments was investigated at 12 weeks. If non-inferiority was demonstrated, superiority was then investigated. After 12 weeks of treatment, the non-inferiority of treatments was demonstrated:

-14 (±0.8) mmHg in the aliskiren group versus -11.6 (±0.8) mmHg in the ramipril group and superiority was investigated and demonstrated: difference -2.3 mmHg, p<0.02.

The Gao 2011 meta-analysis selected studies comparing aliskiren with an ARB II in hypertensive patients, published between 1980 and 2010. The primary efficacy endpoint was the reduction in diastolic blood pressure (DBP) and SBP at the end of the study compared with on inclusion. A total of 9 randomised clinical studies were included in this meta-analysis, with a total of 3,292 patients. The authors observed an absence of a significant difference between aliskiren and the ARB II investigated (losartan, valsartan or irbesartan) in terms of the reduction in blood pressure: difference -0.18 mmHg [-1.07; 10.71], NS.

As combination therapy:

The randomised, double-blind ATLAAST study (Ferdinand 2011) compared the efficacy of the combination aliskiren 300 mg/day + hydrochlorothiazide (HCTZ) 25 mg (after an initial dose of 150/12.5 mg for one week) with amlodipine 10 mg/day (after an initial dose of 5 mg/day for one week), in 332 patients of African origin with stage II hypertension (SBP > 160 mmHg) monitored for 8 weeks. After 8 weeks of treatment, no significant difference was observed in terms of a reduction in blood pressure between the combination aliskiren+HCTZ and amlodipine as monotherapy: -28.61 mmHg in the aliskiren+HCTZ group versus -28.18 mmHg in the amlodipine as monotherapy group, which is a difference of -0.42 [-3.8; 2.9], NS.
6.2. Adverse effects

6.2.1. Data from the re-assessment by EMA

Data from the ALTITUDE study
When the study stopped on 14 December 2011 (available data from submission of dossier) adverse events considered as treatment-related had been observed in 1620/4272 patients (37.9%) in the aliskiren group and 1292/4285 (30.2%) in the placebo group. The most common (> 3%) adverse events were:
- hyperkalaemia: 23.9% versus 16.8%,
- hypotension: 6.3% versus 3.8%,
- renal impairment: 3.6% versus 2.8%.

The final results published on 3 November 2012 (Parving et al1), highlighted the following:
- 563 patients (13.2%) from the aliskiren group and 437 patients from the placebo group (10.2%) discontinued their treatment due to an adverse event (p<0.001),
- The most commonly observed events were:
  - Hyperkalaemia: 39.1% versus 29%, p<0.001,
  - Peripheral oedema: 16.1% versus 15.5%, NS,
  - Hypotension: 12.1% versus 8.3%, p<0.001,
  - Diarrhoea: 9.8% versus 7.3%, p<0.001,
  - Renal impairment: 9.8% versus 8.7%, NS.

Data from PSUR
Periodic pharmacovigilance reports (PSUR 1 to 7) covering the period from 5/03/2007 to 30/09/2011 were submitted by the applicant. Consequently, on 30 September 2011, estimation of the cumulative exposure to RASILEZ was approximately 1,946,000 patient-years.

In total, 18,548 adverse events were observed, including 7,640 that were serious (5,294 unexpected). The most common adverse events were observed in the following organ system classes:
- nervous system disorders (1,714 events, including 591 serious and 460 serious and unexpected), especially: dizziness (299), headache (252), syncope (54), paraesthesia (45), stroke (43), somnolence (39), shaking (33), loss of consciousness (30) and urinary frequency (33).
- renal and urinary disorders (751 events, including 508 serious and 500 serious and unexpected), especially: acute renal failure (108), renal impairment (107), impaired renal function (86) and proteinuria (61).
- cardiac disorders (729 events, including 560 serious and 537 serious and unexpected), especially: palpitations (132), heart failure (51), tachycardia (45), atrial fibrillation (39), bradycardia (34) and arrhythmia (31).

Conclusions:
Analysis of PSUR data and interim results from the ALTITUDE study resulted in EMA re-assessing this proprietary medicinal product and making changes to its SPC, in particular to the following sections (see Appendix 2)*:
- adverse effects: addition of dizziness, hypotension, hyperkalaemia, acute renal failure, changes in renal function and blood creatinine increased.
- contraindications: "the concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²)," and "the combination is not recommended in other patients."

* For other changes to the SPC, refer to Opinion CT-12283 concerning SPC amendments.
6.2.2. Risk management plan

RASILEZ (aliskiren) had its risk management plan updated, in particular to include monitoring of the following "significant" risks:

- Identified risks:
  - diarrhoea,
  - anaphylactic reactions and angioedema,
  - rash,
  - hyperkalaemia,
  - renal impairment (including acute renal failure) and increased blood creatinine,
  - peripheral oedema

- Potential risks:
  - colorectal hyperplasia, including bowel cancer,
  - hypotension,
  - ischemic colitis.

This RMP also identified missing information regarding the effect of aliskiren:
  - in pregnancy,
  - in the paediatric population,
  - in patients with severe renal impairment or with renovascular hypertension,
  - on the reduction in cardiovascular morbidity and mortality.

EMA is currently in the process of updating the RMP.

6.2.3. Data from clinical studies and meta-analyses

**ALLAY study:**
In this study, adverse events were observed in 259/460 patients (56.3%): 91 patients (59.1%) in the aliskiren group, 82 (53.9%) in the losartan group and 86 (55.8%) in the aliskiren + losartan group. The most common (> 5%) adverse events were:

- headache: 9.1% versus 5.3% versus 6.5%,
- nasopharyngitis: 7.1% versus 8.6% versus 7.1%,
- potassium levels < 3.5 mEq/l: 8.1% versus 7.3% versus 4.6%.

**AGELESS study:**
In this study, adverse events were observed in 328/452 patients, (72.6%) in the aliskiren group and 336/444 (75.7%) in the ramipril group. The most common (> 7%) adverse events were:

- headache: 9.3% versus 9%,
- upper respiratory tract infection: 7.7% versus 6.3%,
- dizziness: 7.5% versus 8.3%,
- cough: 4.2% versus 13.3%, p<0.0001.

**Gao meta-analysis:**
In this meta-analysis, no significant difference was observed between aliskiren and the ARB II considered (losartan, valsartan or irbesartan) in terms of the number, the frequency or the severity of adverse events observed.
**ALAAST study:**
In this study, adverse events were observed in 131/332 patients (39.5%): 74 patients (44.6%) in the aliskiren + HCTZ group and 57 (34.3%) in the amlodipine group. The most common (> 3%) adverse events were:
- headache: 3.6% versus 4.2%,
- diarrhoea: 3.6% versus 2.4%,
- nausea: 3.6% versus 2.4%,
- hyperkalaemia: 3.6% versus 1.8%.

**Harel 2012 meta-analysis**
The aim of this meta-analysis was to evaluate the safety of aliskiren used in combination with other renin-angiotensin system inhibitors (ACE inhibitors or sartans) in terms of hyperkalaemia compared with monotherapy.

Document research was carried out on Medline, Embase and the Cochrane database between 1948 and 2011. Studies selected were prospective, randomised, comparative, lasting at least 4 weeks and investigated the incidence of combined treatments in terms of hyperkalaemia or renal impairment.

On this basis, 10 studies were included (7 comparing the combination of aliskiren + sartans versus monotherapy and 3 studies comparing the combination aliskiren + ACEIs versus monotherapies).

The primary efficacy endpoint was hyperkalaemia, defined as a serum potassium concentration > 5.5 mmol/l (mEq/l).

**Results:** the risk of hyperkalaemia was significantly increased in the groups treated with the combination aliskiren + renin-angiotensin system inhibitor (ACEI or sartans) versus the monotherapies:
- combinations versus sartans or ACEI as monotherapy: RR 1.58, 95% CI [1.24; 2.02],
- combinations versus aliskiren as monotherapy: RR 1.67, 95% CI [1.01; 2.79].

**6.3. Interaction with other medicinal products**
Analysis of post-marketing (PSUR) data and the results from the ALTITUDE study have highlighted an increase in the occurrence of hyperkalaemia and renal impairment with aliskiren in combination with other renin-angiotensin system inhibitors (ACEIs and ARB IIIs). Therefore, the "Interaction with other medicinal products" section had been amended and the following wording has been added: The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) and is not recommended in other patients.

Furthermore, in April 2009, the interaction with NSAIDs was added "As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the antihypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients."
6.4. Conclusion

Aliskiren (RASILEZ) has been on the market since 2008 in the indication “treatment of essential arterial hypertension.”

Since its commercialisation, a morbidity and mortality study (the ALTITUDE study) has provided the following new information:

The aim of this study was to compare aliskiren with placebo, and both in combination with a conventional treatment, including an ACEI or an ARB II, in terms of morbidity and mortality in patients with type II diabetes and renal impairment. The primary efficacy endpoint was a combination of cardiovascular death, sudden death after resuscitation, MI or non-fatal stroke, hospitalisation due to heart failure, terminal renal failure or renal-related death and persistent doubling of serum creatinine for at least one month.

This study was stopped at the second interim analysis due to the increase in the aliskiren group:

- in the number of events included in the primary combined endpoint (cardiovascular-related death, sudden death after resuscitation, MI and non-fatal stroke, hospitalisation due to heart failure, terminal renal failure or renal-related death and persistent doubling of serum creatinine for at least one month): 748 patients (17.5%) in the aliskiren group versus 686 (16%) in the placebo group: HR 1.107 [0.996; 1.231], NS.
- an excessive number of strokes (secondary endpoint) observed in the aliskiren group: 144 patients (13.4%) in the aliskiren group and 113 patients (12.6%) in the placebo group, HR 1.29 [1.01; 1.65], p=0.043,
- an excessive number of adverse effects observed in the aliskiren group: hyperkalaemia, hypotension and renal impairment.

Given these results, and following a re-assessment by EMA, contraindications, special warnings for use, interactions with other medicinal products and adverse effects have been added to the Marketing Authorisation for RASILEZ.

After a median follow-up period of 32.9 months:
- The number of adverse events included in the combined primary endpoint observed was: 783 patients (18.3%) in the aliskiren group and 732 (17.1%) in the placebo group: HR 1.08 [0.98; 1.20], NS.
- Stroke (secondary endpoint) was observed in 147 patients (3.4%) in the aliskiren group and 122 patients (2.8%) in the placebo group, HR 1.22 [0.96; 1.55], NS.
- Resuscitated cardiac arrests (secondary endpoint) were observed in 19 patients (0.4%) in the aliskiren group and 8 patients (0.2%) in the placebo group, HR 2.40 [1.05; 5.48], p=0.04.

As no other morbidity and mortality study is currently available, the efficacy of aliskiren (RASILEZ) in terms of morbidity and mortality is yet to be established.

Regarding the efficacy of aliskiren for the interim endpoints,
- One study (ALLAY), showed that the addition of aliskiren to losartan did not provide an additional benefit in terms of a reduction in left ventricular mass in hypertensive patients who are overweight with left ventricular hypertrophy. This study did not highlight any significant difference in terms of a reduction in ventricular mass between aliskiren 300 mg (-4.9 g/m²; 5.4%), losartan 100 mg (-4.8 g/m²; 4.7%) and the combination aliskiren/losartan (-5.8 g/m²; 6.4%) in the group.
- The long-term sustained antihypertensive effect of aliskiren could not be established. The pivotal studies from the Marketing Authorisation dossier and new available data (AGELESS, Gao and ATLAAST) have demonstrated the efficacy of aliskiren, alone and in a combination, on the reduction of blood pressure of hypertensive patients in clinical studies carried out over 6 weeks and up to 12 months (one study). However,
even if data indicates that the antihypertensive effect is sustained in the medium-term, available data for long-term sustained efficacy (> 12 months) are limited.
- Efficacy and safety data for elderly patients are limited (a single specific study on 900 elderly patients > 65 years, who were overweight).

In terms of safety, data from periodic pharmacovigilance reports (PSUR) and the ALTITUDE study also highlighted, especially when aliskiren is combined with another rennin-angiotensin-aldosterone system inhibitor (ACEI or ARB II) in diabetic patients with renal impairment:
- a higher number of strokes and an increase in hypotension and hyperkalaemia type adverse events,
- changes in renal function, including acute renal failure.

These observations led EMA to:
- contraindicate the combination of aliskiren with an ARB II or an ACEI in patients with diabetes or renal impairment (GFR < 60 ml/min/1.73 m²) and to not recommend this combination in other patients,
- add special warnings for use in instances of the combination of aliskiren with an NSAID due to the risk of hyperkalaemia and the negative impact on renal function.

The aim of the RMP for aliskiren is to monitor the significant identified risks (diarrhoea, angioedema and anaphylactic reactions, rash, hyperkalaemia, renal impairment - including acute renal failure - and increase in serum creatinine and peripheral oedema) and potential risks (colorectal hyperplasia, hypotension and ischemic colitis).
In addition, this RMP has identified missing information that the applicant must provide data for and especially that regarding the impact of aliskiren on the reduction of cardiovascular morbidity and mortality.
7.1. Re-assessment of actual benefit

Essential arterial hypertension, due to its complications, can be life-threatening.

This medicinal product is intended as a preventive therapy.

In the majority of hypertensive patients, the therapeutic needs are covered by the use of five categories of antihypertensives (diuretics, ACEIs, ARB II s, calcium inhibitors and beta-blockers), with most active ingredients having demonstrated a benefit in morbidity and mortality in the prevention of cardiovascular events and death from any cause.

Given the results observed from the ALTITUDE study, the morbidity and mortality study that stopped prematurely due to an excessive number of cardiovascular events, especially stroke, and a higher incidence of adverse events already known with aliskiren, (hyperkalaemia, renal impairment, hypotension) observed in the aliskiren (RASILEZ) group compared with placebo, the concomitant use of aliskiren with a renin-angiotensin-aldosterone system (RAAS) blocker, with an ARB II or an ACEI is contraindicated in patients presenting with diabetes or renal impairment (GFR < 60 ml/min/1.73 m$^2$). In cases of double blockage of the RAAS, the efficacy/adverse effects ratio is unfavourable.

In the absence of available data, the use of aliskiren is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m$^2$); its efficacy/adverse effects ratio in these patients is yet to be established.

For other patients, given:
- the long-term efficacy and safety data already available for some antihypertensive treatments in five other therapeutic categories,
- the absence of long-term data available for the renin inhibitor therapeutic category, which includes aliskiren (currently the only molecule in this category with Marketing Authorisation)
- the absence of a demonstration in efficacy for aliskiren in terms of morbidity and mortality,
- the safety profile for aliskiren, especially with common adverse effects (hyperkalaemia and renal impairment) and worrying consequences seen within the scope of the RMP and confirmed through new data available (ALTITUDE study),
- the absence of efficacy and safety data for aliskiren in patients with failed treatment with one or several molecules from the five anti-hypertensive categories,
- the fact that the sustained antihypertensive effect of aliskiren and its long-term safety could not be established due to the limited duration of studies available (≤ 12 months),

the efficacy/adverse effects ratio for aliskiren could not be specifically established.

Given all these points, aliskiren is an antihypertensive that should only be used as a last resort for patients who could not be controlled by any of the other five antihypertensive categories that have a demonstrated efficacy in terms of morbidity and mortality and not treated with another renin-angiotensin system inhibitor (ACEI or ARB II).

Public health benefit:
The public health burden of essential arterial hypertension and cardiovascular diseases, for which it is a risk factor, is substantial.
The reduction in morbidity and mortality attributable to arterial hypertension is a public health need (identified GTNDO* and public health law priority).
However, the existing treatments already help to meet this need.
In light of the available data (in particular that of morbidity and mortality), RASILEZ has no additional impact on reducing morbidity and mortality compared with other
antihypertensives. In the current state of knowledge, it may be considered that RASILEZ does not provide a response to an identified public health need. Consequently, RASILEZ is not expected to benefit public health in this indication.


Given the results from the ALTITUDE study, the actual benefit of aliskiren in hypertensive patients treated with a combination already containing a renin-angiotensin system inhibitor (ACEI or ARB II), which included diabetic patients or those with renal impairment, is inadequate to justify its reimbursement through National Insurance.

In order to not deny other patients who are in potential need (patients not controlled despite using the five categories recommended, used alone or in combination with each other) and not treated with another RAAS inhibitor (ACEI or ARB II), taking into account the recommendations and the contraindications in the Marketing Authorisation, the Transparency Committee considers that the actual benefit of RASILEZ is low for these patients, while waiting for new, specific, more reassuring clinical data for these patients.

### 7.2. Re-assessment of the improvement in actual benefit (IAB)

RASILEZ does not provide an improvement in actual benefit (IAB V) in the management of arterial hypertension in patients not controlled despite using the five categories of antihypertensives (diuretics, ACEIs, ARB IIs, calcium inhibitors and beta-blockers - used alone or in combination with each other) and not treated with another RAAS inhibitor (ACEI or ARB II).

### 7.3. Therapeutic Use

Diet and lifestyle measures are recommended for all hypertensive patients regardless of their blood pressure, with or without an associated drug treatment.

The reduction in cardiovascular risk is, above all, dependant on the lowering in blood pressure, irrespective of the antihypertensive treatment used.

For non-complicated essential arterial hypertension, some thiazide diuretics, some beta-blockers, some calcium inhibitors, some angiotensin converting enzyme inhibitors and some angiotensin II receptor blockers have shown a benefit in cardiovascular morbidity and mortality in clinical studies.

These categories of medicinal products are therefore recommended as first-line therapies in the management of non-complicated essential arterial hypertension.

In the majority of hypertensive patients, the therapeutic needs are covered by the use of the five classes of antihypertensives: diuretics, ACEIs, ARB IIs, calcium inhibitors and beta-blockers, which have demonstrated a benefit in morbidity and mortality in the prevention of cardiovascular events and death from any cause.

The therapeutic use of aliskiren:

Given the efficacy data on blood pressure alone and results observed in the morbidity and mortality study that stopped prematurely due to the observation of an excessive number of cardiovascular events (especially stroke) and adverse events (in particular hyperkalaemia), in the aliskiren group (RASILEZ) compared with placebo, aliskiren can only be used after failure of the other five categories of antihypertensives that have shown efficacy in morbidity

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19 Working group on the management of arterial hypertension, European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), Journal of Hypertension 2007; 25: 1013-85.
and mortality (used alone or in combination with each other) and not treated with another RAAS inhibitor (ARB II or ACEI).

7.4. Target population
The target population of RASILEZ corresponds to patients not controlled by any of the five categories of antihypertensives that have shown efficacy in terms of mortality and morbidity, not treated with a monotherapy or a combination already containing a renin-angiotensin aldosterone system inhibitor (ACEI or ARB II) and taking into account the recommendations and the contraindications of the Marketing Authorisation.

The prevalence of AHT in France is estimated at between 12 and 14 million adult patients.22,23
For information, an unpublished study concerning the methods of managing AHT in general practice (THALES/CEMKA 2010) showed that:
- 77% of patients are receiving an antihypertensive drug treatment,
- nearly 60% of them are treated with a combination of at least two antihypertensives,
- an ACEI or ARB II is prescribed in 43% of prescriptions and in nearly 90% of prescriptions including a set dual-therapy.
The proportion of patients not controlled despite using the five categories of antihypertensives (diuretics, ACEIs, ARB IIs, calcium inhibitors and beta-blockers) and not treated with another RAAS inhibitor is not quantifiable.
Therefore, the target population of RASILEZ cannot be specifically determined.

7.5. Transparency Committee recommendations
The Committee does not recommend continued inclusion for this product on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in hypertensive patients treated with a combination already containing a renin-angiotensin system inhibitor (ACEI or ARB II) and at the dosage in the Marketing Authorisation.

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services for other patients.

In compliance with Articles L.162-17 of the French Social Security Code and L.5123-2 of the French Public Health Code, due to the severity of hypertension in patients for whom the AB of RASILEZ is satisfactory, the Committee recommends that the initial prescription for RASILEZ is made by cardiologists and nephrologists only.

Reimbursement rate: 15% uniquely for hypertensive patients not controlled by any of the five categories of antihypertensives that have demonstrated an efficacy in terms of morbidity and mortality, not receiving a renin angiotensin-aldosterone system inhibitor (ACEI or ARB II).

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Appendix 1

EMA Conclusions

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No. 726/2004, for aliskiren containing products initiated by the European Commission.

- The Committee considered the interim results of the ALTITUDE study and all available data submitted from clinical trials, and safety databases in relation to the overall risk of the treatment of hypertension of patients with aliskiren in combination with ACE inhibitors or ARBs.

- The Committee agreed that the ALTITUDE study has not yet been finalised. However and in view of this limitation, the Committee concluded that due to the study findings the benefit-risk balance for aliskiren when used in diabetic patients receiving ACE inhibitors or ARBs or patients with renal impairment (GFR < 60 ml/min) is considered negative.

- The Committee agreed however, that the results of the ALTITUDE study provided evidence of an increased risk of cardiovascular and renal complications. Considering all the currently available data the Committee considered that it is justified to amend the Product Information for all aliskiren containing medicinal products in the treatment of hypertension in diabetic patients and patients with renal impairment (GFR < 60 ml/min). Therefore the combination of aliskiren with ARBs or ACEI is being contraindicated in patients with diabetes mellitus and in patients with decreased renal function. In addition the Committee agreed that dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an ACE inhibitor or an ARB is therefore not recommended in all other patients.

- The Committee agreed that increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Therefore the Committee recommends the monitoring of the renal function including serum electrolytes if co-administration is considered necessary.

- The Committee concluded that the benefit-risk balance of RASILEZ for hypertension is positive under normal conditions of use, taking into account the restrictions and warnings agreed.

In view of the above, the CHMP has recommended the variation to the terms of the Marketing Authorisation for RASILEZ (see Annex A), for which the relevant sections of the Summary of Product Characteristics, Annex II and Package Leaflet are set out in Annex I, Annex II and III B and subject to the conditions set out in Annex II.
### Appendix 2

**SPC RASILEZ**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Initial Marketing Authorisation (EC decision of 22 August 2007)</th>
<th>EC decision of 22 November 2011</th>
<th>EC decision of 20 April 2012</th>
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</thead>
<tbody>
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### Adverse effects

RASILEZ has been evaluated for safety in more than 7,800 patients, including over 2,300 treated for over 6 months, and more than 1,200 for over one year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. For doses up to 300 mg, treatment with RASILEZ led to an overall incidence of adverse effects comparable to that of the placebo. The adverse effects were generally light in intensity, of a transient nature and did not require discontinuation of treatment in most cases. The most common adverse reaction is diarrhoea.

The incidence of cough was comparable between patients receiving placebo (0.6%) and those receiving RASILEZ (0.9%).

The adverse effects (Table 1) are classified in decreasing order of frequency, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated cases. Within each frequency group, the adverse effects are presented in order of decreasing seriousness.

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<tr>
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<th>Nervous system disorders</th>
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<tbody>
<tr>
<td><strong>Uncommon:</strong> Hyperkalaemia</td>
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<td>Gastrointestinal disorders</td>
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<td>Immune system disorders</td>
<td>Vascular disorders</td>
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<td><strong>Rare:</strong> Hypersensitivity reactions</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td><strong>Uncommon:</strong> Peripheral oedema</td>
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<td>Investigations</td>
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Angioedemas and hypersensitivity reactions occurred during treatment with aliskiren. In controlled clinical studies, angioedemas and hypersensitivity reactions occurred rarely during treatment with RASILEZ with rates comparable to treatment.

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with placebo or with hydrochlorothiazide. Treatment with aliskiren with rates comparable to treatment with placebo or comparators.

In the event of any signs suggesting an allergic reaction (in particular difficulties breathing or swallowing, swelling of the face, the extremities, the eyes, the lips and/or the tongue) patients should discontinue treatment and contact their physician.

In the event of any signs suggesting an allergic reaction (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases was associated with the administration of other medicines known to cause angioedema, including RAAS inhibitors (ACEIs or ARBs).

Hypersensitivity reactions have also been reported during post-marketing experience. In the event of any signs suggesting a hypersensitivity allergic reaction/an angioedema (in particular difficulties breathing or swallowing, rash, itching, urticaria or swelling of the face, the extremities, the eyes, the lips and/or the tongue and dizziness) patients should discontinue treatment and contact their physician.

Laboratory findings
In controlled clinical studies, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of RASILEZ. In clinical studies in hypertensive patients, RASILEZ had no clinically important effects on total cholesterol, HDL-cholesterol, fasting triglycerides, fasting glucose or uric acid.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 percent, respectively) were observed. No patient discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as ACEIs and ARBs.

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<th>Kalaemia: In patients with essential arterial hypertension and treated with RASILEZ as monotherapy, increases in kalaemia were minor and uncommon (0.9% compared with 0.6% with placebo). Nevertheless, during a study in which RASILEZ was used in combination with an ACEI in diabetic patients, increases in kalaemia were more common (5.5%). For this reason, as with all substances that act on the RA system, regular monitoring of electrolytes and renal function is recommended in patients presenting with diabetes, a renal disorder, or heart failure.</th>
<th>Kalaemia: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised. If co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR &lt; 60 ml/min/1.73 m²) and is not recommended in other patients.</th>
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