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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

RASILEZ (aliskiren), **RASILEZ HCT** (aliskiren/hydrochlorothiazide), renin inhibitor, alone or in combination with a diuretic

Insufficient clinical benefit in the treatment of hypertension to justify continued reimbursement

Main points

- RASILEZ has a Marketing Authorisation in the treatment of essential hypertension in adults.
- RASILEZ HCT has a Marketing Authorisation in patients whose blood pressure is not adequately controlled by aliskiren or hydrochlorothiazide used alone.
- New data confirm the absence of benefit of aliskiren relative to placebo in terms of cardiovascular prevention, associated with an increased risk of adverse events (hyperkalaemia, renal impairment, hypotension) regardless of the patient population studied (heart or renal failure patients, elderly patients with other risk factors).
- Aliskiren's safety profile has been regularly re-evaluated in light of the adverse effects observed in studies, with the recent addition of dyspnoea and hyponatremia.

Therapeutic use

- In most patients with hypertension, therapeutic needs are met by using 5 classes of antihypertensives (diuretics, calcium channel blockers, ACE inhibitors, sartans, beta blockers).
  In patients who are not controlled by the medicines in these five classes, used alone or in combination, other classes of antihypertensives that have only shown efficacy in terms of blood pressure reduction can be used: vasodilators, alpha-blockers, central antihypertensives.

- **Role of the medicinal product in the therapeutic strategy**
  Aliskiren is the only representative of the class of renin inhibitors currently available. In light of:
  - demonstrated efficacy only on blood pressure, which is a surrogate endpoint,
  - the absence of benefit of aliskiren relative to placebo in terms of the prevention of cardiovascular events combined with an increased risk of adverse events (hyperkalaemia, renal impairment, hypotension) regardless of the patient population studied (heart or renal failure patients, elderly patients with other risk factors),
  - the numerous alternatives available, especially the 5 aforementioned classes of antihypertensives (diuretics, ACE inhibitors, ARBs, calcium channel blockers and beta blockers), most of the active substances of which have demonstrated a benefit on morbidity and mortality, in terms of the prevention of cardiovascular events and all-cause mortality,
  - aliskiren's safety profile, in particular with angioedema, hyperkalaemia and renal impairment/renal failure, which are major identified risks and are monitored as part of an RMP,
  - aliskiren's safety profile, which is regularly re-evaluated in light of the adverse effects observed in studies, with the recent addition of dyspnoea and hyponatremia,

  the use of aliskiren, alone or in combination with hydrochlorothiazide, could present a lost opportunity for patients. Consequently, RASILEZ and RASILEZ HCT have no role in the therapeutic strategy for patients with hypertension.

Clinical data

- In patients with mild to moderate hypertension, available studies have demonstrated a dose-dependent efficacy of RASILEZ and RASILEZ HCT in reducing diastolic blood pressure (DBP – primary endpoint). The results observed on systolic blood pressure (SBP – secondary endpoint) were consistent with those obtained on DBP.
- The effect of aliskiren on morbidity and mortality has not been demonstrated to date in any of the 4 studies conducted, regardless of the population in the following studies:
- ALTITUDE, conducted in patients with type II diabetes with renal impairment, was stopped prematurely, due to increase in the aliskiren group in:
  - the number of events making up the composite primary endpoint: cardiovascular death, sudden death after resuscitation, non-fatal MI or stroke, hospitalisation due to heart failure, end-stage renal failure or renal-related death, or doubling of blood creatinine levels for at least 1 month. After a median follow-up of 32.9 months, no significant difference was observed versus placebo
  - the 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,
  - the number of adverse effects observed in the aliskiren group: hyperkalaemia, hypotension and renal impairment.
- ASTRONAUT, conducted in heart failure patients, showed that after 6 months of treatment, there was no difference on the composite primary endpoint (cardiovascular death or re-hospitalisation for heart failure) between aliskiren and placebo. These results were confirmed after 12 months of follow-up.
- APOLLO, conducted in patients over 65 years of age with pre-HTA or hypertension with SBP <160 mmHg, showed that after 6 months, results on the composite primary endpoint defined by cardiovascular death, non-fatal MI or heart failure (n = 25 events in total) did not differ between the aliskiren and placebo groups.
- ATMOSPHERE, conducted in patients with heart failure, showed that after a median follow-up of 36.6 months, no significant difference was observed between the treatment groups (aliskiren versus enalapril + aliskiren).
- The safety profile of aliskiren has been regularly re-evaluated given the adverse effects observed in studies, in particular with the addition of:
  - the contraindication of the combination of aliskiren with an ARB or an ACE inhibitor in patients with diabetes or renal failure (GFR < 60 ml/min/1.73 m2) and the recommendation to avoid this combination in other patients,
  - precautions for use in combination with an NSAID, due to the risk of hyperkalaemia and the negative impact on renal function.
  - adverse effects: dyspnoea, hyponatremia.

Benefit of the medicinal product

- The actual benefit* of the medicinal products RASILEZ and RASILEZ HCT is insufficient to justify reimbursement by National Health Insurance.
- Does not recommend continued inclusion on the lists of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 14 December 2016 (CT-15609) and is available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement by National Health Insurance.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.