Health Canada Endorsed Important Safety Information on PrRASILEZ*(aliskiren) and PrRASILEZ HCT* (aliskiren/hydrochlorothiazide)

NOVARTIS

January 18, 2012

Dear Health Care Professional,

Subject: Potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes treated with aliskiren (RASILEZ*) or aliskiren/hydrochlorothiazide (RASILEZ HCT*).

Novartis Pharmaceuticals Canada Inc. ("Novartis"), in collaboration with Health Canada, would like to inform you about important new safety information for aliskiren–containing products following interim results review from the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). Interim results indicated a higher incidence of non-fatal strokes, renal complications (end stage renal disease and renal death), hyperkalemia and hypotension in aliskiren-treated patients.

Aliskiren (RASILEZ*) is currently indicated for the treatment of mild to moderate essential hypertension. It may be used alone or concomitantly with thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin II AT1 receptor blockers or dihydropyridine calcium channel blockers. Aliskiren and hydrochlorothiazide (RASILEZ HCT*) are indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

Analyses of the ALTITUDE interim results from the ALTITUDE study are ongoing. However, pending further analyses, a contra-indication in patients with diabetes taking an ACE inhibitor or an ARB is now advised. The treatment of diabetic patients taking aliskiren-containing products should therefore be reviewed as early as possible, taking the following advice into consideration:

- Aliskiren or aliskiren-containing fixed combination products must not be used in combination with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in patients with diabetes, therefore:
  - Healthcare professionals must stop aliskiren-containing treatment in patients who are diabetic and also taking an ACE inhibitor or an ARB. Alternative antihypertensive treatment should be considered if necessary.
  - Treatment with aliskiren-containing products must not be initiated in diabetic patients who are also taking either an ACE inhibitor or ARB.
- Patients should NOT stop any of these treatments before discussing with a healthcare professional.

Further information on the safety concern

The ALTITUDE study was conducted in type 2 diabetic patients, known to be at risk of fatal and non-fatal cardiovascular and renal events. In this study, Aliskiren 300 mg (or placebo) was given in addition to standard of care, including an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

The 4-year multinational randomized, double-blind, placebo-controlled study was designed to evaluate the potential benefits of aliskiren in reducing the risk of cardiovascular and renal events in more than 8606 patients, including 329 Canadian patients.

The primary endpoint of the ALTITUDE study was the first occurrence of one of the following events: cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, doubling of baseline serum creatinine concentration to above the upper limit of normal (sustained for at least one month), and onset of end stage renal disease or renal death.

The ALTITUDE study was reviewed on a regular basis by a Data Monitoring Committee (DMC), which noted an emergence of imbalance of adverse events only after 18-24 months. The results of that interim analysis are shown in the table below.

ALTITUDE Primary and secondary composite outcomes and each component outcome based on adjudicated events; time-to-event analysis
Randomized Population

Variable	Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)	HR	95% CI	P-value
Primary composite outcome	581 (13.6%)	542 (12.6%)	1123 (13.1%)	1.09	(0.97, 1.22)	0.1663
Secondary composite outcome - CV	444 (10.4%)	396 (9.2%)	840 (9.8%)	1.14	(0.99, 1.30)	0.0664
Secondary composite outcome - renal	166 (3.9%)	180 (4.2%)	346 (4.0%)	0.93	(0.76, 1.15)	0.5178
Component event:						
CV death	179 (4.2%)	162 (3.8%)	341 (4.0%)	1.12	(0.90, 1.38)	0.3110
Resuscitated sudden death	13 (0.3%)	8 (0.2%)	21 (0.2%)	1.64	(0.68, 3.95)	0.2737
Non-fatal MI	90 (2.1%)	88 (2.0%)	178 (2.1%)	1.03	(0.77, 1.39)	0.8302
Non-fatal stroke	112 (2.6%)	85 (2.0%)	197 (2.3%)	1.34	(1.01, 1.77)	0.0439
Unplanned hospitalization for heart failure	150 (3.5%)	155 (3.6%)	305 (3.6%)	0.98	(0.78, 1.23)	0.8716
Onset of ESRD/renal death	72 (1.7%)	60 (1.4%)	132 (1.5%)	1.22	(0.87, 1.72)	0.2518
Doubling of baseline serum creatinine	141 (3.3%)	159 (3.7%)	300 (3.5%)	0.90	(0.71, 1.12)	0.3431
Death from any cause	297 (6.9%)	277 (6.4%)	574 (6.7%)	1.08	(0.92, 1.27)	0.3661

On the basis of preliminary interim analyses, the Data Monitoring Committee concluded that study patients were unlikely to benefit from aliskiren. Furthermore, there was a higher incidence of adverse events related to non-fatal stroke, renal complications (end stage renal disease and renal death), hyperkalemia and hypotension in this high-risk population.

Additional analyses from ALTITUDE are ongoing and the Canadian Product Monograph will be updated in 2012.

Call for Reporting

Healthcare professionals should report any suspected adverse reactions associated with use of aliskiren to Health Canada (See below). Adverse reaction should also be reported to Novartis (See below)

Novartis Pharmaceuticals Canada Inc.
385 Bouchard blvd,
Dorval, Quebec, H9S 1A9
Phone: 1-800-363-8883 (Medical Information)

Any suspected adverse reaction can also be reported to:
Canada Vigilance Program
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701E
Ottawa, Ontario, K1A 0K9
Telephone: 613-957-0337 or Fax: 613-957-0335
CanadaVigilance@hc-sc.gc.ca

To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789

Postage paid labels, the Canada Vigilance Reporting Forms and the Adverse Reaction Reporting Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section. The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate (MHPD)
E-mail: MHPD_DPSC@hc-sc.gc.ca
Tel: 613-954-6522
Fax: 613-952-7738

To change your mailing address or fax number, contact Novartis Pharmaceuticals Canada Inc.

Should you have any questions or require additional information regarding the use of RASILEZ* (aliskiren) or RASILEZ HCT* (aliskiren and hydrochlorothiazide), please contact Novartis Pharmaceuticals Canada Inc., Medical Information Department at 1-800-363-8883.

Sincerely,

Jean-Marie Leclerc, M.D. FRCP(C)
Chief Scientific Officer and Senior Vice-President Clinical and Regulatory Affairs

*RASILEZ and RASILEZ HCT are registered trademarks