SUMMARY OF THE RISK MANAGEMENTPLAN FOR RASILEZ® (ALISKIREN)

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Based on the EU-RMP v15.2 (Approval date: 23 Jan 2023)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risk as well as to prevent or minimize them.

The RMP summary of Rasilez® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Rasilez® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic, Future Health Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Rasilez®.

Summary of risk management plan for Rasilez® (Aliskiren):

This is a summary of the risk management plan (RMP) for Rasilez®. The RMP details important risks of Rasilez®, how these risks can be minimised, and how more information will be obtained about Rasilez® 's risks and uncertainties (missing information).

Rasilez®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rasilez® should be used.

This summary of the RMP for Rasilez® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rasilez®'s RMP.

I. The medicine and what it is used for

Rasilez® is authorised for:

The treatment of essential hypertension in adults (see SmPC for the full indication).

It contains aliskiren as the active substance and it is given by oral route of administration.

Further information about the evaluation of Rasilez®'s benefits can be found in Rasilez®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/documents/overview/rasilez-epar-summary-public_en.pdf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Rasilez®, together with measures to minimise such risks and the proposed studies for learning more about Rasilez®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Rasilez® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rasilez® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded

as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rasilez®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long- term use of the medicine).

List of important risks and missing information	
Important identified risks	• Angioedema • Hyperkalaemia • Renal impairment/renal failure
Important potential risks	• Colorectal hyperplasia • Ischaemic colitis • Stroke
Missing information	• Pregnancy and lactation • Use in paediatric patients • Cardiovascular morbidity and mortality reduction • Use in patients with severe renal dysfunction • Long-term data on aliskiren use with concomitant calcium channel blockers • Long-term data in patients with pre-existing cardiovascular disease • Long-term data in patients with eGFR < 60 ml/min • Long-term data in patients with pre-existing diabetes

II.B Summary of important risks

Angioedema	
Evidence for linking the risk to the medicine	**Aliskiren:** **Post-marketing:** Till the DLP of previous report (30 Sep 2018), 742 cases involving 1,108 events were received for aliskiren from post-marketing sources. Of these 742 cases, 681 were spontaneous reports, five were literature reports, 44 were from PMS and other solicited sources, and 12 were from other sources. Of 1,108 events, 852 were serious and 256 were non-serious. Event outcome was reported as fatal (two), not recovered (62), recovered (585), recovering (93), recovered with sequelae (3) and unknown (363). **CT:**

	Till the DLP of previous report (30 Sep 2018), 80 cases involving 120 events were received for aliskiren from Of the 120 events, 98 were serious and 22 were non-serious. Event outcome was reported as fatal (one), not recovered (15), recovered (84), recovering (11), recovered with sequelae (3) and unknown (6). During the reporting period 1 Oct 2018 to 14 Oct 2022, 5 cases were received for aliskiren from post-marketing sources. All these 5 cases were spontaneous reports. Till the DLP of this report cumulatively 747 cases from post-marketing sources were received for aliskiren.
Risk factors and risk groups	Majority of the reported cases presented only symptoms of angioedema with a clinical diagnosis. These events were mainly mild to moderate in severity. Increased severity/specificity was defined as reports including the following criteria e.g. associated anaphylaxis, bronchospasm, dyspnoea, endotracheal intubation, laryngeal edema, laryngospasm, mechanical ventilation, respiratory distress, tracheostomy, wheezing, postural hypotension, death, a life-threatening seriousness criterion or involved hospitalization. There were several cases with one or more of these symptoms when aliskiren alone or in combination was administered. The current label appropriately characterizes and addresses the severity of the risk. Generally, African-Americans have a higher risk of development of angioedema. Data from CTs and from spontaneously reported cases no special group could be identified with a higher than average risk. Due to lack of epidemiological data about the risk of angioedema among hypertensive patients and specifically among those treated with aliskiren and/or with other antihypertensive medications it is unknown if there is a specific group of patients in higher risk. Based on literature patients with previous experience of angioedema or other allergic reactions may be in a higher risk than others.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4 and 4.8 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Hyperkalaemia	
Evidence for linking the risk to the medicine	**Aliskiren:** **Post-marketing:** Till the DLP of previous report (30 Sep 2018), 531 cases involving 544 events were received for aliskiren from post-marketing sources. Of these 531 cases, 367 were spontaneous reports, 31 were literature reports, 108 PMS report and 25 were from other sources. Of 544 events, 342 were serious and 202 were non-serious. Event outcome was reported as fatal (five), not recovered (21), recovered (209), recovering (75), recovered with sequelae (two) and unknown.(232) . **CT:** Till the DLP of previous report (30 Sep 2018), 171 cases involving 175 events were received for aliskiren from CT. During the reporting period 1 Oct 2018 to 14 Oct 2022, 2 cases were received for aliskiren from post-marketing sources. Of these 2 cases, one was literature report and the remaining was spontaneous report. Till the DLP of this report cumulatively 533 cases from post-marketing sources were received for aliskiren.
Risk factors and risk groups	Patients with pre-existing renal diseases, reduced renal function, cardiac diseases, diabetes, those concomitantly treated with NSAIDs, other RAAS blockers, other drugs increasing serum potassium level (i.e. potassium sparing diuretics, supplements etc.), elderly patients. Hyperkalaemia could be silent in the majority of the cases without immediate clinical consequences and diagnosed only with routine or targeted laboratory investigation. However, in cases where it reaches certain individual threshold it could become life-threatening, leading to cardiac arrhythmias or sudden death.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2, 4,3, 4.4, 4.5, 4.8, 5.1 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Renal impairment/renal failure	
Evidence for linking the risk to the medicine	**Aliskiren:** **Post-marketing:** Till the DLP of previous report (30 Sep 2018), 1,877 cases involving 2,874 events were received for aliskiren from post-marketing sources. Of these 1,877 cases, 1,276 were spontaneous reports, 49 were literature reports, 484 were from PMS and other solicited sources, and 68 were from other sources. Of 2,876 events, 1,989 were serious and 887 were non-serious. Event outcome was reported as fatal (60), not recovered (270), recovered (678), recovering (384), recovered with sequelae (20) and unknown (1464). **CT:** Till the DLP of previous report (30 Sep 2018) 1,054 cases involving 1,507 events were received for aliskiren from CT. Of the 1,507 events, 1,471 were serious and 36 were non-serious. Event outcome was reported as fatal (183), not recovered (299), recovered (490), recovering (323), recovered with sequelae (57) and unknown (155). During the reporting period 01 Oct 2018 to 14 Oct 2022, 5 cases were received for aliskiren from post-marketing sources. Of these 5 cases, one was literature report, one was spontaneous report and remaining three cases were from other sources. Till the DLP of this report cumulatively 1,882 cases from post-marketing sources were received for aliskiren.
Risk factors and risk groups	Patients with pre-existing renal diseases, reduced renal function, cardiac diseases, diabetes, clinically significant diarrhoea, those concomitantly treated with NSAIDs, other RAAS blockers, other nephrotoxic drugs.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2, 4,3, 4.4, 4.5, 4.8, 5.1 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Colorectal hyperplasia	
Evidence for linking the risk to the medicine	**Aliskiren:** **Post-marketing:** Till the DLP of previous report (30 Sep 2018), 139 cases involving 179 events were received for aliskiren from post-marketing sources. Of these 139 cases, 55 were spontaneous reports, four were literature reports, 79 were from PMS, and one was from other sources. Of 179 events, 163 were serious and 16 were non-serious. Event outcome was reported as fatal (19), not recovered (23), recovered (47), recovering (22) and unknown (68). **CT:** Till the DLP of previous report (30 Sep 2018), 502 cases involving 679 events were received for aliskiren from CT. Of the 679 events, 628 were serious and 51 were non-serious. Event outcome was reported as fatal (82), not recovered (76), recovered (351), recovering (82), recovered with sequelae (25) and unknown (63). During the reporting period 01 Oct 2018 to 14 Oct 2022, two literature cases were received for aliskiren from post-marketing sources. Till the DLP of this report cumulatively 141 cases from post-marketing sources were received for aliskiren.
Risk factors and risk groups	No specific risk group has been identified. Colorectal hyperplasia could be manifested as malignant tumor with a high mortality. However currently there is no evidence that aliskiren would have any causative effect on colorectal hyperplasia.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 5.3 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Ischaemic colitis	
Evidence for linking the risk to the medicine	**Aliskiren:** **Post-marketing:** Till the DLP of previous report (30 Sep 2018), 13 cases involving 14 events were received for aliskiren from post-marketing sources. Of these 13 cases, eight were spontaneous reports and six were PMS report. All the reported events (14) were assessed as serious. Event outcome was reported as fatal (3), recovered (1), recovering (2) and unknown (8). **CT:** Cumulatively till the DLP of this report, 17 cases involving 19 events were received for aliskiren from CT. All the reported events (19) were serious. Event outcome was reported as fatal (8), not recovered (1), recovered (8), recovering (1), and unknown (1). During the reporting period from 01 Oct 2018 till 14 Oct 2022, no case report was identified. Till the DLP of this report cumulatively, 13 cases from post-marketing sources were received for aliskiren.
Risk factors and risk groups	Patients with decreased intestinal blood flow. Ischaemic colitis severity could range from mild transient occurrence with diarrhoea to serious life-threatening or even fatal cases due to prolonged ischemia and necrosis of the colon.
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** No safety concerns have been observed from the clinical trials and post- marketing safety experience. This potential risk will continue to be monitored according to routine pharmacovigilance practices. The SmPC may be updated if new patterns develop during on-going safety reviews. Legal status: Prescription only medicine **<u>Additional risk minimisation measures:</u>** None

Stroke	
Evidence for linking the risk to the medicine	**Aliskiren:** **Post-marketing:** Till the DLP of this report, 478 cases involving 641 events were received for aliskiren from post-marketing sources. Of these 478 cases, 256 were spontaneous reports, two were literature reports, 218 were from PMS and other solicited sources, and two were from other sources.Of 641 events, 632 were serious and nine were non-serious. Event outcome was reported as fatal (56), not recovered (50), recovered (169), recovering (62), recovered with sequelae (57) and unknown (247). **CT:** Cumulatively till the DLP of this report, 798 cases involving 1090 events were received for aliskiren from CT. Of the 1,090 events, 1,082 were serious and eight were non-serious. Event outcome was reported as fatal (191), not recovered (98), recovered (388), recovering (198), recovered with sequelae (169) and unknown (46). During the reporting period 01 Oct 2018 to 14 Oct 2022, six spontaneous cases were identified. Till the DLP of the this report cumulatively, 484 cases from post-marketing sources were received for aliskiren.
Risk factors and risk groups	Common causes of ischaemic stroke are: Thrombosis, Lacunar stroke (small vessel), large vessel thrombosis, Dehydration, Embolic occlusion; Artery-to-artery: Carotid bifurcation, Aortic arch, Arterial dissection; Cardioembolic: Atrial fibrillation, Mural thrombus, Myocardial infarction, Dilated cardiomyopathy, Valvular lesions, Mitral stenosis, Mechanical valve, Bacterial endocarditis; Paradoxical embolus, Atrial septal defect, Patent foramen ovale, Atrial septal aneurysm, Spontaneous echo contrast. Drugs such as cocaine, amphetamine and oral contraceptives, constitute uncommon causes of ischaemic stroke. For hemorrhagic stroke, aneurysmal subarachnoid hemorrhage and hypertensive intracranial hemorrhage are two important causes. Intracranial hemorrhages associated with anticoagulant therapy can occur.
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 4.4, 5.1 Legal status: Prescription only medicine **<u>Additional risk minimisation measures:</u>** None

Pregnancy and lactation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.6 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Use in paediatric patients	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 PL section 2 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Use in patients with severe renal dysfunction	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, 4.8, 5.2 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Cardiovascular morbidity and mortality reduction	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 5.1 and 5.2 Legal status: Prescription only medicine **Additional risk minimisation measures:** None

Long term data on concomitant CCB use	
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** This missing information is not presented in the SmPC. Causal relationship has not been established. The SmPC may be updated if new patterns develop during on-going safety reviews. Legal status: Prescription only medicine **<u>Additional risk minimisation measures:</u>** None

Long term data in patients with pre-existing cardiovascular disease	
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 5.1 and 5.3 Legal status: Prescription only medicine **<u>Additional risk minimisation measures:</u>** None

Long term data in patients with eGFR < 60 ml/min	
Risk minimisation measures	**<u>Routine risk minimisation measures:</u> Aliskiren:** SmPC sections 4.3 and 5.1 Legal status: Prescription only medicine **<u>Additional risk minimisation measures:</u>** None

Long term data in patients with pre-existing diabetes	
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 4.2, 4.3, 4.4 and 5.1 Legal status: Prescription only medicine **<u>Additional risk minimisation measures:</u>** None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Rasilez®.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Rasilez®.