Swiss Summary of the Risk Management Plan

For

Livazo

Active Substance: Pitavastatin

Version 1.0, 22 March 2023
Based on Version 6.0, Core RMP, 06 December 2021

Marketing Authorisation Holder: Recordati AG

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

This RMP summary for Livazo is a concise document and does not claim to be exhaustive.

As the core RMP is an international document, this RMP 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 marketing authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Livazo in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Recordati AG, the Marketing Authorisation Holder, is fully responsible for the accuracy and correctness of the content of the published summary RMP of Livazo.

Summary of risk management plan for Livazo (Pitavastatin)

This is a summary of the risk management plan (RMP) for Livazo. The RMP details important risks of Livazo, and how more information will be obtained about Livazo risks and uncertainties (missing information).

The Livazo summary of product characteristics (SmPC) and the package leaflet presents the essential information to healthcare professionals and patients on how Livazo should be used.

I. The medicine and what it is used for

Livazo is authorised for Primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combined (mixed) dyslipidaemia when response to diet and other non-pharmacological measures is inadequate. (see the SmPC for the full indication). Livazo contains Pitavastatin as the active substance and it is for oral use only and should be swallowed whole. Livazo (Pitavastatin) can be taken at any time of the day with or without food. It is desirable that the patient takes the tablet at the same time each day. Livazo therapy is generally more effective in the evening due to the circadian rhythm of lipid metabolism

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

The important risks of Livazo, together with measures to minimise such risks and the proposed studies for learning more about Livazo'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, within the package leaflet and SmPC addressed to patients and healthcare professionals;

  The Livazo SmPC and leaflet contain relevant warnings, precautions and advice on the correct use of the product.

- Important advice on the packaging;

  The packaging includes storage conditions and advise to keep out of the reach of children.

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

  Livazo is marketed in pack sizes that are consistent with the recommended dosage and the pack quantity is limited to avoid abuse and ensure product safety.

- 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.

  Livazo is only available on prescription that can be renewed.

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

If important information that may affect the safe use of Livazo is not yet available, it is listed under ‘missing information’ below:

II.A List of important risks and missing information

Important risks of Livazo 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 Livazo. 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	➢ *Rhabdomyolysis (including myalgia, muscle disorders, myopathy and associated renal disorder)* ➢ *Liver disorder (including increased transaminases, hepatic function abnormal and jaundice)*
Important potential risks (including class effect)	➢ *Interstitial lung disease (class effect)*
Missing information	➢ *No*

II.B Summary of important risks

Important identified risk: Rhabdomyolysis (including myalgia, muscle disorders, myopathy and associated with renal disorder)

The incidence of Rhabdomylosis has been derived from Phase II and Phase III studies and post-marketing experience (including LIVS-01 study and Japan non-interventional paediatric study) and analysis has been based on the following references:

1. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized habdomyolysis in patients treated with lipid lowering drugs. JAMA. 2004 Dec 1; 292(21):2585-2590.

2. Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. Am Fam Physician. 2002 Mar 1; 65(5):907-912.

3. Arora R, Liebo M, Maldonado F. Statin-induced myopathy: the two faces of Janus. J. Cardiovasc. Pharmacol. Ther. 2006 Jun; 11(2):105-112.

4. Tiwari A, Bansal V, Chugh A, Mookhtiar K. Statins and myotoxicity: a therapeutic limitation. Expert Opin Drug Saf. 2006 Sep; 5(5):651-666.

5. Draeger A, Monastyrskaya K, Mohaupt M, Hoppeler H, Savolainen H, Allemann C, et al. Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia. J. Pathol. 2-006 Sept; 210 (1); 94-102.

6. AHA/ACC/NHLBI guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Nat Lipid Ass. 2014.

7. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolaemia or severe hyperlipidemia: a multi-centre, randomized, placebo-controlled trial. J.Pediatr.2003; 142:74-80.

8. Lebenthal Y, Horvath A, Dziechciarz, P. Szajewska et al. Are treatment targets for hypercholesterolemia evidence based? Systematic review and metaanalysis of RCTs. Arch Dis Child. 2010 Sept; 95(9):673-80.

9. Vuorio A, Kuoppala J, Kovanen PT et al. Statins for children with familial hypercholesterolemia. Cochrane Database Syst Rev. 2014; 7

10. Jose J, Saravu K, Shastry BA. Atorvastatin-induced early-onset rhabdomyolysis in a patient with nephrotic syndrome. Am J Health Syst Pharm. 2007 Apr 1; 64(7):726-9.

11. O'Gorrman CS, Higgins MF, O'Neil MB. Systematic review and metaanalysis of statins for heterozygous FH in children: evaluation of cholesterol changes and side effects. Pediatr Cardiol. 2009 May; 30(4):482-9.

12. Braamskamp MJA, Kusters DM, Avis HJ et al.: Long-term Statin Treatment in Children with Familial Hypercholesterolaemia: More Insight into Tolerability and Adherence. Pediatr Drugs 2015; 17: 159-166.

13. Stein EA, Illingworth DR, Kwiterovich PO, Liacouras CA, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia. A randomized controlled trial. JAMA 1999; 281: 137- 144.

14. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Diseases in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007; 115(14):1948-1967.

15. Muscal E. Rhabdomyolysis. eMedicine 2015. Available at http://emedicine.medscape.com/article/1007814-overview. Accessed 30 August 2016

16. Mannix R, Tan ML, Wright R, Baskin M. Acute Pediatric Rhabdomyolysis: Causes and Rates of Renal Failure. Pediatrics 2006; 118 (5): 2119-2125.

Adults

Based on a review of case reports, older age, female sex, low body mass index, hypothyroidism, diabetes mellitus, and impaired renal or hepatic function have been cited as potential risk factors for rhabdomyolysis, but these have not been confirmed by clinical trials or observational studies [Graham DJ et al., 2004(1)].

Children

In a randomised placebo controlled study of lovastatin, there were infrequent, sporadic, and non-sustained CK elevations exceeding 5xULN throughout the study, which were generally associated with vigorous or unusual exercise [Stein EA et al., 1999(13)]. Vigorous exercise, particularly contact sports or weightlifting, may cause physiological increases in CK [McCrindle et al., 2007(14)].

Rhabdomyolysis may occur in infants, toddlers, and adolescents who have inherited enzyme deficiencies of carbohydrate or lipid metabolism or who have inherited myopathies, such as Duchenne muscular dystrophy and malignant hyperthermia. Other significant paediatric aetiologies include infections, trauma, metabolic conditions, and muscle diseases [Muscal, 2015(15)]. In a retrospective review at a tertiary care paediatric centre review spanning 10 years, viral myositis accounted for most cases in patients aged 0-9 years, whereas trauma was the leading diagnosis in patients aged 9-18 years [Mannix et al., 2006(16)].

Routine risk minimisation measures:

Special warnings and precautions against myopathy and rhabdomyolysis in section 4.4 of the SmPC and listed in section 4.8 of the SmPC.
Prescription only medicine
Additional risk minimisation measures:
NA

Additional pharmacovigilance activities:
None

Important identified risk: Liver disorder (including increased transaminases, hepatic function abnormal and jaundice)
Incidence has been derived from Phase II and Phase III studies and post-marketing experience (including LIVS-01 study and Japan non-interventional paediatric study) and analysis has been based on the following references: 1. De Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation 2002, 106:2231-2237. 2. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolaemia or severe hyperlipidemia: a multi-centre, randomized, placebo-controlled trial. J.Pediatr.2003; 142:74-80. 3. Stein EA, Illingworth DR, Kwiterovich PO, Liacouras CA et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. JAMA 1999, 281:137- 144. 4. Hedman M, Matikainen T, Fohr A, et al. Efficacy and safety of pravastatin in children and adolescents with heterozygous FH: a prospective clinical follow up study. J Clin Endocrinol Metab.2005; 90:1942-1952. 5. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N. Engl J Med.2006; 354:731-739. 6. Lebenthal Y, Horvath A, Dziechciarz, P. Szajewska et al. Are treatment targets for hypercholesterolemia evidence based? Systematic review and metaanalysis of RCTs. Arch Dis Child. 2010 Sept; 95(9):673-80. 7. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familia hypercholesterolemia. Cochrane Database Syst Rev. 2014; 7: CD006401. 8. Braamskamp MJA, Kusters DM, Avis HJ et al.: Long-term Statin Treatment in Children with Familial Hypercholesterolaemia: More Insight into Tolerability and Adherence. Pediatr Drugs 2015; 17: 159-166. 9. Molleston JP, Fontana RJ, Lopez MJ et al. for the Drug-Induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. J. Pediatr. Gastroenterol. Nutr 2011; 53: 182-9.
Adults Risk groups or risk factors are also dependent on the nature of the liver disorder, but alcohol abuse is a major risk factor. Children No data are available.
Routine risk minimisation measures Dosage individualisation by patients in section 4.2 Contraindication in patients with active liver disease in section 4.3 Special warnings and precautions against liver disorder in section 4.4 of the SmPC and listed in in section 4.8 of the SmPC Prescription only medicine Additional risk minimisation measures: NA
Additional pharmacovigilance activities: None

Important identified risk: Interstitial lung diseases
Incidence has been derived from Phase II and Phase III studies and post-marketing experience (including LIVS-01 study) and analysis has been based on the following references: 1 Walker T, McCaffery J, Steinfort C. Potential link between HMG-CoA reductase inhibitor (statin) use and interstitial lung disease. MJA 2007; 186:91-94 2 Liebhaber MI, Wright RS, et al. Polymyalgia, Hypersensitivity Pneumonitis and Other Reactions in Patients Receiving HMG-CoA Reductase Inhibitors: A Report of Ten Cases. Chest 1999; 115: 886-889 3 Thomeer MJ, Costabel U et al. Comparison of registries of interstitial lung diseases in three European countries. Eur Respir J 2001; 18: Suppl. 32, 114s–1 4 Xu JF. Statins and pulmonary fibrosis: The Potential Role of NLRP3 Inflammasome Activation. Am J Res Crit Care Med, 2012; Jan; 28(1):26-35 5 Nathan N, Taam RA, Epaud R et al. A national internet-linked based database for pediatric interstitial lung disease: the French network. Orphanet J Rare Dis 2012; 7: 40-51 6 Griese M, Haug M, Brasch F et al. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. Orphanet J Rare Dis 2009; 4: 26-37
Adults Risk factors for interstitial lung disease with statins are not known. Children Risk factors for interstitial lung disease with statins are not known.
Routine risk minimisation measures No specific description in the CCDS Prescription only medicine Additional risk minimisation measures: NA
Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

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

There are no planned or ongoing additional Pharmacovigilance studies/activities in the Pharmacovigilance Plan, or efficacy studies which are specific obligations and/or conditions of the Marketing Authorisation or other efficacy/effectiveness studies.

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

No studies were conditions of the marketing authorisation in Switzerland.