Part VI: Summary of the Risk Management Plan

Summary of risk management plan for ONCASPAR (pegaspargase)

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

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

This summary of the RMP for ONCASPAR 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 ONCASPAR's RMP.

I. The medicine and what it is used for

ONCASPAR is authorised for acute lymphoblastic leukaemia (see SmPC for the full indication). It contains Pegaspargase as the active substance and it is given by an injection of infusion.

Further information about the evaluation of ONCASPAR's benefits can be found in ONCASPAR's EPAR, including in its plain-language summary, available on the EMA website.

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

Important risks of ONCASPAR, together with measures to minimise such risks and the proposed studies for learning more about ONCASPAR'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 through signal detection, 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 ONCASPAR is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ONCASPAR are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 ONCASPAR. 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).

Table 33. List of Important Risks and Missing Information

Important identified risks	Hypersensitivity (Including Severe hypersensitivity and Anaphylactic shock) Pancreatitis Haemorrhage Thromboembolic events Hepatotoxicity Hyperammonaemia Embryotoxicity and teratogenicity
Important potential risk	Immunogenicity
Missing information	Adverse events with a long latency

II.B Summary of important risks

Table 34. Important Identified Risk– Hypersensitivity (including Severe Hypersensitivity and Anaphylactic shock)

Evidence for linking the risk to the medicine	Hypersensitivity has been reported in clinical trials and scientific and medical literature.
Risk factors and risk groups	The likelihood of occurrence of allergic reactions increases with the number of doses administered. However, rarely, allergic reactions may occur even with the first injection of pegaspargase. Patients with the previous experience of allergic reaction to L-asparaginase or to ONCASPAR are at increased risk of repeated allergic reaction. Risk factors for the drug-induced hypersensitivity reactions may be drug-related (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or antibiotics are notorious for their immunogenicity), treatment regimen-related (intermittent and repeated administrations can be more sensitising than an uninterrupted treatment; parenteral route is considered the most immunogenic), host-related (most studies show that women are more often affected than men, ratio 2:1; it is often reported that children are less affected than adults; however, other studies present similar incidences in paediatric and adults populations), or underlying disease-related (e.g., asthmatics have higher probability of reaction to certain drug groups). [23]

Table 34. Important Identified Risk– Hypersensitivity (including Severe Hypersensitivity and Anaphylactic shock)

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3 – Patients with hypersensitivity to the active substance or excipients are contraindicated. SmPC Section 4.4 – Recommendations to monitor for hypersensitivity reactions for an hour after administration and to have treatments available. SmPC Section 4.8 PL Section 2 – Patients should not use ONCASPAR if they are allergic to pegaspargase or to any of the other ingredients. Patients should notify their doctor if they have had serious allergic reactions to other forms of asparaginase. They should also notify their doctor if they are also receiving vincristine. PL Section 4 – Patients should notify their doctor immediately if they have any symptoms of severe allergic reactions. **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 35. Important Identified Risk – Pancreatitis

Evidence for linking the risk to the medicine	Pancreatitis has been reported in clinical trials and scientific and medical literature.
Risk factors and risk groups	Several factors can increase the risk of pancreatitis, including: gallstones, alcohol abuse, and high level of triglycerides in the blood.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3 – Patients with a history of pancreatitis, including related to prior L-asparaginase are contraindicated. SmPC Section 4.4 – Recommendations to monitor serum amylase and/or lipase levels frequently for early signs of pancreatic inflammation. SmPC Section 4.8 PL Section 2 – Patients should not use ONCASPAR if they have ever had pancreatitis. Patients should notify their doctor if they have abdominal pain. PL Section 4 – Patients should notify their doctor immediately if they have any symptoms of pancreatitis. **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 36. Important Identified Risk – Haemorrhage

Evidence for linking the risk to the medicine	Coagulopathy, which can lead to haemorrhage, has been reported in clinical trials and scientific and medical literature.
Risk factors and risk groups	The risk factors include previous acute haemorrhagic reaction in association with L-asparaginase therapy, concomitant coagulation-inhibiting therapy (e.g., NSAIDs).

Table 36. Important Identified Risk – Haemorrhage

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3 – Patients with a history of serious haemorrhagic events with prior L-asparaginase are contraindicated. SmPC Section 4.4 – Recommendations to monitor coagulation parameters regularly, especially when other medications with pro-/anti-coagulant effects are given concomitantly. Patients with marked decreases in fibrinogen or antithrombin III can be considered for replacement therapy. SmPC Section 4.5 – Caution when medicines with pro-/anti-coagulant effects are given concomitantly. SmPC Section 4.8 PL Section 2 – Patients should not use ONCASPAR if they have ever had serious bleeding following asparaginase therapy. Patients should notify their doctor if they suffer from a bleeding disorder. They should also notify their doctor if they are also receiving any drugs with anticoagulant effects. PL Section 4 – Patients should notify their doctor immediately if they have severe bleeding or bruising. **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 37. Important Identified Risk – Thromboembolic events

Evidence for linking the risk to the medicine	Coagulopathy, which can lead to thromboembolic events, has been reported in clinical trials and scientific and medical literature.
Risk factors and risk groups	Factor V mutations, activated protein C resistance or reduced serum levels of protein S, antithrombin III or protein C represent risk factors for thrombosis.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3 – Patients with a history of serious thrombosis with prior L-asparaginase are contraindicated. SmPC Section 4.4 – Recommendations to monitor coagulation parameters regularly, especially when other medications with pro-/anti-coagulant effects are given concomitantly. SmPC Section 4.5 – Caution when medicines with pro-/anti-coagulant effects are given concomitantly. SmPC Section 4.8 PL Section 2 – Patients should not use ONCASPAR if they have ever had blood clots following asparaginase therapy. Patients should notify their doctor if they have ever had serious blood clots. They should also notify their doctor if they are also receiving prednisone. PL Section 4 – Patients should notify their doctor immediately if they have any blood clots. **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 38. Important Identified Risk – Hepatotoxicity

Evidence for linking the risk to the medicine	Hepatotoxicity has been reported in clinical trials and scientific and medical literature.
Risk factors and risk groups	Combination with other hepatotoxic substances, especially if the patient has a pre-existing hepatic dysfunction.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3 – Patients with severe hepatic impairment are contraindicated SmPC Section 4.4 – Caution should be given when Oncaspar is given in combination with hepatotoxic products (e.g., tyrosine kinase inhibitors), especially if there is pre-existing hepatic impairment. Patients should be monitored for changes in liver function parameters. There is an increased risk of hepatotoxicity in patients >18 years of age. SmPC Section 4.5 - Patients are not recommended to take oral contraceptives due to hepatotoxicity SmPC Section 4.8 SmPC Section 5.3 PL Section 2 – Patients should notify their doctor if they have had poor liver function or are using other medicines which may harm the liver. PL Section 4 – Patients should notify their doctor immediately if they have any problems with their liver. **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 39. Important Identified Risk – Hyperammonaemia

Evidence for linking the risk to the medicine	Hyperammonaemia has been reported in clinical trials, the post-marketing setting and in scientific literature.
Risk factors and risk groups	Patients who are older or have hepatic impairment may be at greater risk of developing symptomatic hyperammonaemia.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 – Intravenous administration may cause serum levels of ammonia to sharply rise after administration. If there are symptoms of hyperammonaemia, ammonia levels should be monitored closely. SmPC Section 4.8 PL Section 4 – Patients should notify their doctor immediately if they have any symptoms of hyperammonaemia **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 40. Important Identified Risk – Embryotoxicity and Teratogenicity

Evidence for linking the risk to the medicine	Embryotoxicity and teratogenicity have been reported in scientific and medical literature.
Risk factors and risk groups	Pre-clinical results suggest that exposure during 1st trimester poses the highest risk for the foetus.

Table 40. Important Identified Risk – Embryotoxicity and Teratogenicity

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 – ONCASPAR should not be used during pregnancy unless clinically required. Breast-feeding should be discontinued during treatment of ONCASPAR. SmPC Section 5.3 PL Section 2 – If patients are pregnant or breast-feeding, think they may be pregnant, or are planning to have a baby, they should ask their doctor for advice. Contraception (other than oral contraceptives) should be used during ONCASPAR treatment and for 6 months after discontinuation. Breast-feeding should be discontinued during treatment with ONCASPAR. **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 41. Important Potential Risk – Immunogenicity

Evidence for linking the risk to the medicine	A potential for immunogenicity, defined as development of binding and/or neutralising antibodies to the product is associated with all therapeutic proteins.
Risk factors and risk groups	Prior exposure to native *E. coli* asparaginase increases the development of anti-PEG-asparaginase antibodies. It was reported that > 65% of patients who had developed anti-asparaginase antibodies to native *E. coli* asparaginase also had antibodies to PEG-asparaginase. However, almost 40% of these patients were PEG-asparaginase naive, suggesting that the IgG antibodies may crossreact. [54] Tong *et al.* found a high incidence of inactivation of PEG-asparaginase (22% clinical allergy and 8% silent inactivation) in the intensification phase because of antibody development against native *E coli* asparaginase, which was used in induction. [55]
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 – Low asparaginase activity levels may be due to potential neutralising anti-asparaginase antibodies. In such cases, a switch to a different asparaginase preparation should be considered. SmPC Section 4.8 SmPC Section 5.3 **Additional risk minimisation measures:** No additional risk minimisation activities.

Table 42. Missing Information – Adverse events with a long latency

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 **Additional risk minimisation measures:** No additional risk minimisation activities.

II.C Post-Authorisation Development Plan

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

The following study (investigator-sponsored trial) is condition of the marketing authorisation:

Table 43. Studies Which are Conditions of the Marketing Authorisation

Study name	Purpose of the study
CAALL-F01: a French protocol for the treatment of acute lymphoblastic leukemia (ALL) in children and adolescents	- For children and adolescents with standard or medium risk ALL, the study has two primary objectives: 1) to assess the superiority in terms of PK at D33 of the fractionated scheme; 2) to assess the equivalence in the tolerance of the 2 schemes (from D12 of induction to D49) - In the High/Very High Risk group two primary objectives have been defined: 1) to assess the PK at D33; 2) to assess the toxicity of the intensified scheme from D12 of induction to D49

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

There are no other studies required for ONCASPAR.