Imfinzi®

50 mg/ml, Concentrate for solution for infusion

Summary of the Risk Management Plan (RMP) for Imfinzi® (durvalumab)

RMP Version 1.0, 16 August 2017

Document Date: 03 August 2018
Summary of the risk management plan (RMP) for Imfinzi® (durvalumab)

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 risks as well as to prevent or minimise them.

The RMP summary of Imfinzi® 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 Imfinzi® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AstraZeneca AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Imfinzi®.

Overview of disease epidemiology

Non-small cell lung cancer (NSCLC) (which represents 85% to 90% of all lung cancers) comprises a heterogeneous group of histologic types, with the most frequent types being adenocarcinomas, squamous cell carcinomas, and large cell carcinomas, representing approximately 40%, 25% to 30%, and 10% to 15% of lung cancers, respectively.

The most recent worldwide data from the International Agency for Research on Cancer (IARC) has reported lung cancer as the most common type of cancer diagnosed, with 41.5% of incident cases having occurred in developed countries.

The IARC reports that, on a worldwide basis, there were 1'893'078 patients alive with a history of a previously diagnosed lung cancer in 2012. According to IARC in the EU-28, 68.3% of incident lung cancer cases occurred in men, which was more than twice the occurrence in women (2012).

Locally advanced NSCLC is defined as Stage III NSCLC based on the most recent International Association for the Study of Lung Cancer (IASLC)/Union for International Cancer Control (UICC) TNM staging system (7th edition; IASLC Staging Manual in Thoracic Oncology). Stage III disease comprises approximately 30% of the NSCLC diagnoses.

The risk factors for NSCLC include tobacco, environmental tobacco smoke, family history and genetic factors, occupational factors and radiation risk, air pollution, and inflammation and infection.

Summary of treatment benefits

At present, no treatment options exist for patients with locally advanced, unresectable, NSCLC whose disease has not progressed after chemoradiation. Patients are instead kept under surveillance and monitored without further therapeutic options treatment until progression – which is, in most cases, metastatic disease.

The PACIFIC study is an ongoing, randomized, double-blind, placebo-controlled, pivotal Phase III study in the durvalumab clinical program. It is designed to evaluate the efficacy and safety of durvalumab compared to placebo in patients with locally advanced, unresectable, NSCLC whose disease has not progressed after platinum-based concurrent chemoradiation. The primary objective is to assess the efficacy of durvalumab compared with placebo in terms of progression-free survival (PFS) and overall survival (OS) (co-primary endpoints).

Durvalumab is administered as intravenous infusion at a dosage of 10 mg/kg every two weeks. In the PACIFIC study 473 patients received durvalumab and 236 patients received placebo. Treatment duration was limited to 12 months. Durvalumab treatment resulted in a 48% reduction in the overall risk of progression or death. The median PFS was 16.8 months in the
durvalumab group compared with 5.6 months in the placebo group. Data on OS are not yet mature.

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC addressed to patients and HCPs
- 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 (eg. with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures. In the case of durvalumab, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 durvalumab is not yet available, it is listed under “missing information” below.

**List of important risks and missing information**

Important risks of durvalumab 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 durvalumab. 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 (eg, on the long-term use of the medicine).

**Table 1 - Important risks and missing information**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-mediated pneumonitis</td>
<td>Immune-mediated pancreatitis</td>
<td>Patients with moderate or severe hepatic impairment</td>
</tr>
<tr>
<td>Immune-mediated hepatitis</td>
<td>Other potential immune-mediated adverse reactions</td>
<td>Patients with severe renal impairment</td>
</tr>
<tr>
<td>Immune-mediated colitis or diarrhoea</td>
<td></td>
<td>Patients with prior Grade ≥3 imAE while receiving immunotherapy, including anti-CTLA-4 treatment or any unresolved imAE &gt;Grade 1</td>
</tr>
<tr>
<td>Immune-mediated hypothyroidism</td>
<td></td>
<td>Patients with pre-existing autoimmune disease</td>
</tr>
<tr>
<td>Immune-mediated hyperthyroidism</td>
<td></td>
<td>Patients with pre-existing active infection including tuberculosis, hepatitis B, hepatitis C, or HIV</td>
</tr>
<tr>
<td>Immune-mediated adrenal insufficiency</td>
<td></td>
<td>Patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab</td>
</tr>
</tbody>
</table>
Summary of important risks

### Table 2 - Important identified risk: immune-mediated pneumonitis

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Immune-mediated pneumonitis has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class. On the MRL strain background, PD-L1 KO mice developed fatal pneumonitis and myocarditis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors specific for immune-mediated pneumonitis associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing inflammatory processes in the lung could be risk factors for immune-mediated pneumonitis of durvalumab. In the stage III lung cancer population, lung inflammation is relatively common due to the effects of smoking such as COPD, underlying lung cancer, and radiation therapy. Symptomatic radiation pneumonitis occurred in 15% to 40% of patients receiving concurrent chemoradiation therapy for locally advanced lung cancer.</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
  - SmPC Section Undesirable effects  
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated pneumonitis  
  Additional risk minimisation measures:  
  - Educational materials for HCPs and patients/carers |

### Table 3 - Important identified risk: immune-mediated hepatitis

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Immune-mediated hepatitis has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class. In PD-L1 KO mice, total CD8 T cell numbers increased dramatically, had an activated phenotype, and survived as a consequence of reduced apoptosis. Accelerated experimental autoimmune hepatitis was observed in PD-L1 KO mice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors specific for immune-mediated hepatitis associated with the anti-PD-1/PD-L1 are unknown. It is conceivable that any pre-existing inflammatory processes in the liver (eg, hepatitis of any aetiology) could be risk factors for immune-mediated hepatitis.</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
  - SmPC Section Undesirable effects  
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated hepatitis  
  Additional risk minimisation measures:  
  - Educational materials for HCPs and patients/carers |

### Table 4 - Important identified risk: immune-mediated colitis or diarrhoea

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Immune-mediated colitis or diarrhoea has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class. PD-L1-deficient mice are highly susceptible to mouse models of inflammatory bowel disease/colitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors specific for immune-mediated colitis or diarrhoea associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing inflammatory processes in the gastrointestinal system (eg, history of diarrhoea and inflammatory bowel disease) could be risk factors for immune-mediated colitis or diarrhoea of durvalumab.</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
  - SmPC Section Undesirable effects  
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated colitis or diarrhoea  
  Additional risk minimisation measures:  
  - Educational materials for HCPs and patients/carers |
### Table 5 - Important identified risk: immune-mediated hypothyroidism

**Evidence for linking the risk to the medicine**
Immune-mediated hypothyroidism has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with anti-PD-1/PD-L1 drug class.

**Risk factors and risk groups**
Risk factors specific for immune-mediated hypothyroidism/thyroiditis associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing inflammatory processes in the thyroid gland could be risk factors for immune-mediated thyroiditis with consequent hypothyroidism.

**Risk minimisation measures**
- Routine risk minimisation measures:
  - SmPC Section Undesirable effects
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated hypothyroidism
- Additional risk minimisation measures:
  - Educational materials for HCPs and patients/carers

### Table 6 - Important identified risk: immune-mediated hyperthyroidism

**Evidence for linking the risk to the medicine**
Immune-mediated hyperthyroidism/thyroiditis has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class.

**Risk factors and risk groups**
Risk factors specific for immune-mediated hyperthyroidism/thyroiditis associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing inflammatory processes in the thyroid could be risk factors for immune-mediated thyroiditis with consequent hyperthyroidism.

**Risk minimisation measures**
- Routine risk minimisation measures:
  - SmPC Section Undesirable effects
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated hyperthyroidism
- Additional risk minimisation measures:
  - Educational materials for HCPs and patients/carers

### Table 7 - Important identified risk: immune-mediated adrenal insufficiency

**Evidence for linking the risk to the medicine**
Immune-mediated adrenal insufficiency has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class.

**Risk factors and risk groups**
Risk factors specific for immune-mediated adrenal insufficiency associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing subclinical or clinical inflammatory processes in the adrenal gland could be risk factors for immune-mediated adrenal insufficiency.

**Risk minimisation measures**
- Routine risk minimisation measures:
  - SmPC Section Undesirable effects
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated adrenal insufficiency
- Additional risk minimisation measures:
  - Educational materials for HCPs and patients/carers

### Table 8 - Important identified risk: immune-mediated hypophysitis or hypopituitarism

**Evidence for linking the risk to the medicine**
Immune-mediated hypophysitis or hypopituitarism has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class.

**Risk factors and risk groups**
Risk factors specific for immune-mediated hypophysitis or hypopituitarism associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing subclinical or clinical inflammatory processes in the pituitary gland could be risk factors for immune-mediated hypophysitis or hypopituitarism.

**Risk minimisation measures**
- Routine risk minimisation measures:
  - SmPC Section Undesirable effects
  - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated hypophysitis or hypopituitarism
- Additional risk minimisation measures:
  - Educational materials for HCPs and patients/carers
### Table 9 - Important identified risk: immune-mediated type 1 diabetes mellitus

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Immune-mediated T1DM has been observed in clinical trials with durvalumab. In non-obese diabetic mice, PD-L1 blockade or gene deletion rapidly precipitates diabetes, while pancreatic overexpression of PD-L1 is protective against diabetes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors for T1DM associated with immune checkpoint inhibitors are unknown. In the general population, susceptibility haplotypes in the HLA class region II are considered the principal susceptibility markers for T1DM. Other studies have found a tendency for metabolic syndrome and greater genetic (HLA-associated) disease in patients with high GADA titre compared with patients with low GADA titre.</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
- SmPC Section Undesirable effects  
- SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated T1DM  
Additional risk minimisation measures:  
- Educational materials for HCPs and patients/carers |

### Table 10 - Important identified risk: immune-mediated nephritis

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Immune-mediated nephritis has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class. In PD-L1 KO mice, a significant increase in PD-1 positive T cells was noted in the kidney, and in autoimmune-prone NZB/W mice PD-L1, the blockade accelerated nephritis in mouse models of nephritis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors specific for immune-mediated nephritis associated with immune checkpoint inhibitor are unknown. It is conceivable that pre-existing subclinical or clinical inflammatory processes in the kidneys could be the risk factors for immune-mediated nephritis.</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
- SmPC Section Undesirable effects  
- SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated nephritis  
Additional risk minimisation measures:  
- Educational materials for HCPs and patients/carers |

### Table 11 - Important identified risk: immune-mediated rash or dermatitis

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Immune-mediated rash or dermatitis has been observed in clinical trials with durvalumab. It is biologically plausible and consistent with the anti-PD-1/PD-L1 drug class. The PD-1 KO mice model showed that PD-1 regulates drug-induced dermatitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors specific for immune-mediated rash or dermatitis associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing subclinical or clinical inflammatory processes in the skin could be the risk factors for immune-mediated rash or dermatitis.</td>
</tr>
</tbody>
</table>
| Risk minimisation measures | Routine risk minimisation measures:  
- SmPC Section Undesirable effects  
- SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated rash or dermatitis  
Additional risk minimisation measures:  
- Educational materials for HCPs and patients/carers |
### Table 12 - Important identified risk: immune-mediated myocarditis

| Evidence for linking the risk to the medicine | Rare cases of immune-mediated myocarditis have been observed in clinical trials with durvalumab. PD-1 KO mice developed autoimmune dilated cardiomyopathy, which is driven by autoantibodies directed against troponin I. Furthermore, in a number of mouse models of experimentally induced myocarditis, PD-1/PD-L1 signalling was demonstrated to be key in preventing cardiac inflammation and damage. |
| Risk factors and risk groups | Risk factors specific for immune-mediated myocarditis associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing subclinical or clinical inflammatory processes in the heart could be the risk factors for immune-mediated myocarditis. |
| Risk minimisation measures | Routine risk minimisation measures:  
   - SmPC Section Undesirable effects  
   - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage immune-mediated myocarditis  
Additional risk minimisation measures:  
   - Educational materials for HCPs and patients/carers |

### Table 13 - Important identified risk: infusion-related reaction

| Evidence for linking the risk to the medicine | Infusion-related reaction has been observed in clinical trials with durvalumab. This is a common risk for medications administered via infusion. |
| Risk factors and risk groups | Risk factors specific for infusion-related reaction with anti-PD-1/PD-L1 are unknown. |
| Risk minimisation measures | Routine risk minimisation measures:  
   - SmPC Section Undesirable effects  
   - SmPC Sections Posology and method of administration and Special warnings and special precautions for use where advice is given on how to identify and manage infusion-related reaction |

### Table 14 - Important potential risk: immune-mediated pancreatitis

| Evidence for linking the risk to the medicine | There were no confirmed cases of immune-mediated or serious pancreatitis observed with durvalumab monotherapy, except for a single case of non-serious pancreatitis without identified alternative aetiologies reported in the PACIFIC study. Immune-mediated pancreatitis has been observed in other PD-1/PD-L1 agents. |
| Risk factors and risk groups | Risk factors specific for immune-mediated pancreatitis associated with anti-PD-1/PD-L1 are unknown. It is conceivable that pre-existing subclinical or clinical inflammatory processes in the pancreas could be the risk factors for immune-mediated pancreatitis. |
| Risk minimisation measures | Routine risk minimisation measures:  
   - SmPC Section Special warnings and special precautions for use for other immune-mediated adverse reactions  
   - SmPC Sections Posology and method of administration and Special warnings and special precautions for use for monitoring and management of an imAE |

### Table 15 - Important potential risks: other potential immune-mediated adverse reactions

| Evidence for linking the risk to the medicine | Other immune-mediated adverse reactions have been rarely observed in clinical trials with other PD-1/PD-L1 agents. They can be potentially serious or life-threatening for the individual patient and require careful monitoring, early recognition, timely intervention by withholding/discontinuation of durvalumab, and appropriate medical intervention, including systemic corticosteroids therapy. |
| Risk factors and risk groups | It is conceivable that pre-existing subclinical or clinical inflammatory processes in all organs could be the risk factors for immune-mediated reactions. |
| Risk minimisation measures | Routine risk minimisation measures:  
   - SmPC Section Special warnings and special precautions for use for other immune-mediated adverse reactions  
   - SmPC Sections Posology and method of administration and Special warnings and special precautions for use for monitoring and management of an imAE |
Table 16 - Missing information: patients with moderate or severe hepatic impairment

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Sections Posology and method of administration and Pharmacokinetic properties</td>
</tr>
</tbody>
</table>

Table 17 - Missing information: patients with severe renal impairment

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Sections Posology and method of administration and Pharmacokinetic properties</td>
</tr>
</tbody>
</table>

Table 18 - Patients with prior Grade ≥3 imAE while receiving immunotherapy, including anti-CTLA-4 treatment or any unresolved imAE >Grade 1

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Section Pharmacodynamic properties/Mechanism of Action</td>
</tr>
<tr>
<td></td>
<td>• SmPC Sections Posology and method of administration and Special warnings and special precautions for use for monitoring and management of an imAE</td>
</tr>
</tbody>
</table>

Table 19 - Missing information: patients with pre-existing autoimmune disease

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Section Pharmacodynamic properties/Mechanism of Action</td>
</tr>
<tr>
<td></td>
<td>• SmPC Sections Posology and method of administration and Special warnings and special precautions for use for monitoring and management of an imAE</td>
</tr>
</tbody>
</table>

Table 20 - Missing information: patients with pre-existing active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Section Pharmacodynamic properties/Mechanism of Action</td>
</tr>
</tbody>
</table>

Table 21 - Missing information: patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Section Pharmacodynamic properties/Mechanism of Action</td>
</tr>
</tbody>
</table>

Summary of risk minimisation measures by safety concern

All medicines have a product information which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. The measures in these documents are known as routine risk minimisation measures.

The product information for durvalumab can be found on [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch). To ensure HCPs and patient/carers are made aware of signs, symptoms and risks of important imAEs and have immediate access to additional information the following materials will be made available in Switzerland:

- Educational material for HCPs
- Educational material for Patients/Carers
- Patient alert card

The measures in these documents are known as additional risk minimisation measures.

Post-authorisation development plan

Studies that are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation for durvalumab.

Other studies in post-authorisation development plan

There are no studies required for durvalumab.