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# Summary of the risk management plan (RMP) for Portrazza (necitumumab)

This is a summary of the risk management plan (RMP) for Portrazza, which details the measures to be taken in order to ensure that Portrazza is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Portrazza, which can be found on Portrazza's EPAR page.

## Overview of disease epidemiology

Portrazza is used to treat adults with squamous non-small cell lung cancer (NSCLC) that express a certain type of protein on their surface known as epidermal growth factor receptor (EGFR).

Lung cancer is the 4th most frequently diagnosed cancer in the European Union (EU) with 313,000 new cases diagnosed in 2012. Squamous NSCLC accounts for 25% to 30% of all lung cancers and usually does not show symptoms until the tumour has spread too far to be cured. Factors known to increase chances of lung cancer are smoking tobacco, advanced age, male gender, pollutants and radon, and other kinds of lung disease.

## Summary of treatment benefits

A main study of 1,093 patients with advanced squamous non-small cell lung cancer showed that adding Portrazza to gemcitabine and cisplatin chemotherapy can lead to a modest improvement in survival. In this study, patients treated with Portrazza in addition to chemotherapy lived on average 1.6 months longer than those treated with chemotherapy alone (11.5 months versus 9.9 months).

Most of the patients (95%) had cancer cells with EGFR. There was no improved survival in patients with non-EGFR cancer cells.

## Unknowns relating to treatment benefits

There are no data on necitumumab use in pregnant or breast-feeding women and only limited data on necitumumab use in patients with severe kidney or moderate to severe liver disorders. There is also a lack of data concerning activity against some biomarker-defined tumour subtypes (EGFR and KRAS and other downstream markers).

## Summary of safety concerns

### *Important identified risks*

| Risk | What is known | Preventability |
|---|---|---|
| Blood clots in the veins (venous | Portrazza can cause blood clots in veins. Symptoms may include | It is important to be aware of this risk and to start treatment to dissolve the |

| Risk | What is known | Preventability |
|---|---|---|
| thromboembolic events [VTEs]) | swelling, pain and tenderness of the limb, difficulty breathing, chest pain, and an abnormal heartbeat.<br><br>Blood clots in veins occur in approximately 8% of patients. The side effects were severe in approximately 4% of patients. | blood clots as soon as possible after they occur. Patients at risk should receive appropriate preventive treatment before starting Portrazza<br><br>The doctor will discuss any preventive measures that may be needed. Patients should be told to go to their doctor or to a hospital if they develop symptoms such as shortness of breath, chest pain and swelling in the limbs.<br><br>Blood thinners should be considered before giving Portrazza especially in patients who might be more at risk for clots. The decision to take blood thinners should be made after carefully looking at all the risks for that patient, including the risk of bleeding into a tumour or bleeding from a blood vessel inside a tumour.<br><br>The doctor should carefully think about the use of Portrazza in patients with a history of blood clots. Caution should be exercised in patients who already have risk factors for blood clots. |
| Allergic reactions to Portrazza (infusion-related reactions [IRRs]) | Allergic reactions (infusion-related reactions) may occur during treatment with Portrazza.<br><br>The most common reactions that have occurred with Portrazza were hypersensitivity (allergic reaction) and infusion related reactions.<br><br>Approximately 1.5% of patients receiving Portrazza have had an allergic reaction, with only 0.4% of patients having a severe reaction. | Patients should talk to their doctor about the need for any preventive measures or early treatment. The doctor or nurse will check for side effects during a patient's infusion. If a patient has a severe infusion-related reaction, the doctor may adjust the dose of Portrazza, or may stop Portrazza treatment.<br><br>Patients will be watched while receiving Portrazza and if needed, treatment will be given if signs of allergic reaction are seen.<br><br>In patients who have previously experienced mild hypersensitivity or infusion-related reaction to Portrazza, premedication with a corticosteroid (such as a cortisone cream) and an antipyretic (medicine that reduces fever) in addition to an antihistamine (for treating allergic reactions) is |

| Risk | What is known | Preventability |
|---|---|---|
| | | recommended.<br><br>Trained personnel, medicines and equipment for treating severe infusion reactions should be available during infusions of Portrazza. The clinic or the hospital must also have equipment available to treat the patients if they go into shock or if their heart stops beating. |
| Blood clots in the arteries (arterial thromboembolic events [ATEs]) | Portrazza can cause blood clots in the arteries. Symptoms may include swelling, pain and tenderness of the limb, difficulty breathing, chest pain, and an abnormal heartbeat.<br><br>The most common blood clots seen in the arteries were in the form of a stroke (not enough blood flow to the brain) and myocardial infarction (heart attack).<br><br>In cases of a stroke, the symptoms can include difficulty talking or moving the muscles of the mouth, weakness in the arms or legs on one side, and difficulty speaking or remembering things.<br><br>For cases of heart attack (not enough blood flow to the heart), the symptoms can include pain in the chest, or along the left arm, sudden weakness or faintness, shortness of breath, and not being able to walk or support yourself.<br><br>Approximately 4.3% of patients receiving Portrazza in studies developed blood clots in the arteries; and approximately 3% of these blood clots were considered severe. | Most blood clots in an artery do not have early warning signs, so it is important to be aware of this risk and to start treatment to dissolve the blood clots early.<br><br>Patients should be told to go to their doctor or to a hospital if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. The doctor will discuss any preventative measures that may be needed.<br><br>Medicines to prevent clotting should be considered especially in patients who might be more at risk for clots. The decision to give blood thinners should be made after carefully looking at all the risks for patients, including risks like bleeding into the tumour or damage to the blood vessel wall in or near the tumour.<br><br>The doctor should carefully think about using Portrazza in patients with a known history of blood clots. Caution should be taken in patients who already have risk factors for blood clots<br><br>Patients should call their doctor or nurse immediately if symptoms such as swelling, pain, and a sore arm or leg, or coughing and shortness of breath occur. The patient's doctor will discuss with them the need for any preventive measures. |
| Very low magnesium levels | Levels of magnesium in the blood can fall during treatment with Portrazza. Low levels of magnesium | Patients should be monitored and tested for blood salts (electrolytes), including magnesium before and after |

| Risk | What is known | Preventability |
|---|---|---|
| | are seen in 81% of patients given Portrazza, and may be severe in about 19%. | receiving treatment with Portrazza. If the patient's level of these substances drops too low, supplements are recommended. |
| Severe skin rash/skin reaction | Skin reactions were reported with Portrazza and they occurred mainly during the first cycle of treatment.<br><br>Skin-related reactions occur in about 78% of patients given Portrazza and are usually mild to moderate. Severe skin reactions were seen in approximately 6% of patients.<br><br>Symptoms of severe skin reactions may include acne-like skin conditions and skin rash, dry skin, itchy skin, breaks in the skin, an infection around the nail, and redness, swelling or loss of skin on the palms of the hands or soles of the feet. The skin rash commonly resembles acne and often involves the face, upper chest and back, but can affect any area of the body.<br><br>Most of these side effects usually disappear over time after the end of Portrazza therapy. | Preventive skin treatments including skin moisturisers, sun screens, topical steroid cream (1% hydrocortisone) and an oral antibiotic (e.g. doxycycline) must be considered.<br><br>If a patient has a severe skin reaction, the doctor may recommend an adjustment of the dose of Portrazza, or stop treatment with Portrazza. |

***Important potential risks***

| Risk | What is known |
|---|---|
| Developmental and reproductive reactions (DART) | The effects of Portrazza in pregnant women and on fertility are unknown. Medicines such as Portrazza affect EGFR (epidermal growth factor) which is important for the developing embryo. Portrazza should therefore not be used during pregnancy or in women not using effective contraception unless the potential benefits outweigh the risks to the unborn baby. |
| Cardiorespiratory disorders (disorders of the heart and airways) | Cases of cardiorespiratory arrest and sudden death were observed in patients treated with Portrazza. The causes of these deaths and their relationship to treatment were not always known. Because lung cancer usually happens in older people, who may also have heart disease or lung problems, they may be at a higher risk of cardiorespiratory arrest and sudden death. Treatment with Portrazza may increase this risk. |

***Missing information***

| Risk | What is known |
|---|---|
| Use in pregnancy and lactation | Using Portrazza during pregnancy or while breastfeeding is not recommended. There have been no studies using Portrazza during pregnancy or while breastfeeding. |
| Biomarker-defined tumour subtypes (EGFR and KRAS and other downstream markers) | Patients with certain tumour types may not respond well to treatment with Portrazza. Physicians may perform specific tests before start of treatment to assess whether Portrazza is suitable. |

## Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Portrazza can be found on Portrazza's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Portrazza's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

***Blood clots in veins or arteries (venous thromboembolic events or arterial thromboembolic) events and cardiorespiratory disorders***

| **Risk minimisation measure**: Educational materials for doctors |
|---|
| Objective and rationale: To provide information on the risk of blood clots and reports of cardiorespiratory disorders |
| Description: Doctors will be sent educational materials telling them the key conditions for the safe use of Portrazza, including information on cardiorespiratory disorders and on blood clots in veins and arteries. Doctors will be advised to consider treatment to reduce or prevent blood clots for patients with a high risk of blood clots. |

## Planned post-authorisation development plan

***List of studies in post-authorisation development plan***

| Study / activity (including study number) | Objectives | Safety concerns / efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Physician/oncologist knowledge survey | Assessment of the physician/oncologist (cancer specialist) understanding of key conditions for the safe use of Portrazza. | Primarily:<br>• Thromboembolic events<br>• Cardiorespiratory disorders<br>In addition:<br>Hypersensitivity/infusion related reactions<br>• Severe skin reactions<br>• Severe electrolyte abnormalities | Planned | Final report will be submitted within 12 months of end of data collection.<br>Submission date will depend on time of launch and market uptake. |
| Observational Prospective Post-authorisation safety study | Assessment of the incidence, severity and outcome of the targeted safety concerns | All serious life-threatening identified and potential risks for Portrazza treatment in the approved indication | Planned | Final report will be submitted within 12 months of end of data collection. |
| Exploratory analyses of biomarker status in the necitumumab clinical development programme of 4 Phase 1b/2 clinical trials | Assessment of EGFR protein expression status of patients and EGFR and/or KRAS mutation status of patients in the studies | Address missing information on activity in biomarker defined subtypes | Planned | Q4 2018 (3 clinical trials)<br>July 2019 (1 clinical trial) |

***Studies which are a condition of the marketing authorisation***

None

## Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 01-2016.