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Summary of the risk management plan (RMP) for Imbruvica (ibrutinib)

This is a summary of the risk management plan (RMP) for Imbruvica, which details the measures to be taken in order to ensure that Imbruvica 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 Imbruvica, which can be found on Imbruvica's EPAR page.

Overview of disease epidemiology

Imbruvica is a cancer medicine that is used to treat two types of blood cancer: chronic lymphocytic leukaemia and mantle cell lymphoma.

Chronic lymphocytic leukaemia (a cancer of a type of white blood cells called B lymphocytes) is a rare disease that affects around 4 in 100,000 people per year in the Western world. It mainly affects elderly people, typically around 70 years of age. The course of the disease is highly variable, and low-risk patients may expect to live for more than 10 years compared with 2 years in high-risk patients.

Mantle cell lymphoma belongs to a group of cancers called non-Hodgkin lymphomas that affect B lymphocytes. It is also a rare disease that affects less than 1 in 100,000 people throughout the world. Mantle cell lymphoma occurs more frequently in older adults, the average age at diagnosis being in the mid-60s. It is more common in men than women and white people are at a higher risk than black people.

Summary of treatment benefits

In a main study involving 391 patients with chronic lymphocytic leukaemia that did not respond to or had come back after previous treatment, Imbruvica was shown to be more effective than ofatumumab (another cancer medicine) at delaying progression of the cancer. After 1 year of treatment, around 66% of patients receiving Imbruvica were still alive with their disease not having progressed compared with around 6% of patients receiving ofatumumab. Imbruvica was also more effective than ofatumumab in the subgroup of patients with certain genetic mutation in their cancer cells (17p deletion/TP53 mutation) which makes them unsuitable for chemotherapy (medicines to treat cancer) and immunotherapy (medicines that stimulate the immune system to kill cancer cells).

Imbruvica was also investigated in a main study involving 111 patients with mantle cell lymphoma that did not respond to or had come back after previous treatment. In this study Imbruvica was not compared with any other treatment. Results of the study showed Imbruvica to be effective, with around 68% of patients having either a complete or partial response to treatment: 21% of patients had a complete response (i.e. disappearance of all signs of cancer following treatment) and 47% had a partial response (i.e. the patient improved but some signs of the disease remained). The average duration of response to treatment was 17.5 months.

Unknowns relating to treatment benefits

There is either no or only limited information about the use of Imbruvica in certain subgroups of patients including patients with viral hepatitis, severe liver disease, severe kidney disease or significant heart disease.

In mantle cell lymphoma there are currently no data comparing Imbruvica treatment with any other available treatments.

Based on results of the studies conducted with the medicine, there is no evidence to suggest that results with Imbruvica would be different in patients of different ethnic origins.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increased blood thickness and tendency for certain types of cells in the blood to clump together (leukostasis)	Cases of leukostasis have been reported in patients treated with Imbruvica (in less than 1 patient in 100). Leukostasis cause serious problems by blocking blood vessels and stopping oxygen getting to the body's tissues, especially in the brain and lungs. This may cause headache, blurred vision, strokes or mini-strokes or bleeding inside the brain, and shortness of breath.	This risk is preventable by the doctor monitoring the patient's blood counts regularly. However, if it occurs, it is an emergency, and needs to be treated in hospital by a specialist who can give treatment to reduce the number of cells and unblock the blood vessels. The doctor should also consider temporarily interrupting treatment with Imbruvica.
Increased bleeding (haemorrhage)	Bleeding can occur either outside or inside the body. If bleeding occurs inside the brain it may cause difficulty moving, speaking, understanding or seeing, sudden severe headache, seizure, and numbness or weakness in any part of the body. Cases of bleeding have been reported very commonly in patients treated with Imbruvica (in more than 1 patient in 10).	Patients should tell their doctor if they experience any increase in bleeding or symptoms of bleeding, or if they are taking any medicines or supplements that increase the risk of bleeding such as aspirin and other NSAIDs (non-steroidal anti-inflammatory drugs such as ibuprofen), blood thinners such as warfarin, and supplements such as fish oil, Vitamin E or flax seeds. Treatment with Imbruvica should be interrupted for a few days in patients having surgery.

Important potential risks

Risk	What is known
Interactions with other medicines (drug-drug	Certain medicines can increase or decrease the amount of ibrutinib in the patient's blood. Patients should tell their doctor about all medicines they are taking.

Risk	What is known
interactions)	Patients should not take Imbruvica with grapefruit or Seville oranges; this includes eating them, drinking the juice or taking a supplement that might contain them. This is because they affect the way Imbruvica is processed in the body and can increase its amount in the blood. Patients should not take Imbruvica with St John's wort. This is because it can increase the rate at which Imbruvica is processed thereby decreasing its amount in the blood.
Low red blood cell counts (anaemia)	Anaemia occurs when the number of healthy red blood cells in the body is too low. As red cells carry oxygen to all the body's tissues, many of the symptoms of anaemia are caused by decreased oxygen delivery to tissues and organs. Cases of anaemia have been reported very commonly in patients treated with Imbruvica (in more than 1 patient in 10). In case of anaemia, treatment with Imbruvica may have to be interrupted. It is important that patients have regular blood tests as advised by the doctor to identify anaemia early.
Low white blood cell counts (neutropenia)	Neutropenia is an abnormally low level of neutrophils, a type of white blood cell that fights infections. People who have neutropenia are at increased risk of serious infections. Cases of neutropenia have been reported very commonly in patients treated with Imbruvica (in more than 1 patient in 10). If neutropenia occurs, treatment with Imbruvica may have to be interrupted. It is important to have regular blood tests as advised by the doctor to identify neutropenia early.
Low blood platelet counts (thrombocytopenia)	Platelets are blood components that help the blood to clot after injury. Symptoms of low blood platelet counts include severe bleeding, which may be fatal if not treated. However, sometimes the only symptoms are simple bruising. Typically, a low platelet count is the result of a medical condition, like leukaemia, or certain medicines. Cases of thrombocytopenia have been reported very commonly in patients treated with Imbruvica (in more than 1 patient in 10). If thrombocytopenia occurs, treatment with Imbruvica may have to be interrupted. It is important that patients have regular blood tests as advised by the doctor to identify and manage thrombocytopenia early.
Infections	People who have a low white blood cell count are at increased risk of infection. Infections (including serious and fatal infections) have occurred in patients treated with Imbruvica. If infections occur, treatment with Imbruvica may have to be interrupted and appropriate treatment with anti-infectives started. Monitoring the patient's blood counts helps to identify patients at risk of developing an infection.
Irregular heart beat (cardiac arrhythmia)	Patients treated with Imbruvica may be at an increased risk of developing abnormal heart rhythms (when the heart is beating quickly or unevenly (irregularly)). If abnormal heart rhythms appear during Imbruvica treatment, the doctor will treat this as appropriate.

Risk	What is known
Severe problems affecting the stomach and gut (severe GI disorders)	Patients treated with Imbruvica may be at an increased risk of feeling sick (nausea), vomiting or changes to bowel movements, such as diarrhoea.
Other cancers (other malignancies)	Chemotherapy works by killing cancer cells; however, normal cells can also be damaged in ways that may later make them become cancerous. This may lead to new tumours that are not related to the first cancer that was treated, which may occur months or even years after initial treatment. Preventing other cancers involves avoiding or restricting the treatments that increase the risk of causing cancers.
Allergic reactions to Imbruvica (hypersensitivity)	An allergic reaction to Imbruvica may cause difficulty breathing, swelling of the lips, itching or rash. Imbruvica should not be used if allergy to ibrutinib itself or other ingredients is known or suspected.
Harm to the unborn child (teratogenicity)	No information from clinical trials is available on the use of Imbruvica during pregnancy. Based on animal tests, Imbruvica may cause harm to the unborn child if women become pregnant while taking Imbruvica. It is important that women who could become pregnant use an effective method of contraception while being treated with Imbruvica.
Side effects caused by the breakdown of cancer cells (tumour lysis syndrome)	Patients treated with Imbruvica may develop a serious potentially fatal problem caused by the breakdown products of dying cancer cells (uric acid, potassium and phosphorus). It is most likely to occur 12 to 72 hours after the treatment has been taken. Preventative measures should be taken as necessary and treatment should be started early for identified cases.
Eye disorders	Eye problems could occur in patients treated with Imbruvica. They may be more likely to occur in older people, with exposure to sunlight, and in people who smoke cigarettes or drink alcohol.
Kidney failure (renal failure)	Patients treated with Imbruvica may have an increased risk of developing kidney failure, especially if they already have risk factors such as diabetes, high blood pressure, heart disease, or a family history of kidney disease, and if they are over 60 years old. Kidney disease may also be more likely in persons from certain ethnic groups. Other risk factors include diseases in which the body is attacked by its own immune system (such as lupus), infections, kidney stones, blockage of the lower water passages, and taking medicines that affect the way the kidneys work.
High blood pressure (hypertension)	Patients treated with Imbruvica, especially elderly ones, may be at an increased risk of developing high blood pressure.

Missing information

Risk	What is known
Use in children	The safety of Imbruvica in children has not been studied.
Use during breastfeeding	It is not known whether this medicine passes into breast milk or if it can harm the baby. Women should not breastfeed while they are taking this medicine.
Use in patients with significant heart disease	Imbruvica was not studied in patients with significant heart disease. Imbruvica is to be used with caution in these patients and these patients need to be monitored throughout treatment.
Use in patients with severe kidney disease (Use in patients with severe renal impairment)	Very little of the ibrutinib, the active substance of Imbruvica, that a patients takes is eliminated by the kidney. Therefore it is unlikely that having kidney disease will lead to problems caused by having more ibrutinib in the body than intended. However as ibrutinib also gets changed into other molecules (metabolites) inside the body, some of which are eliminated by the kidney, it is recommended that patients with severe renal disease are monitored carefully by their doctor.
Use in patients with severe liver disease (Use in patients with severe hepatic impairment)	Ibrutinib is eliminated by the liver so it is likely that liver disease will lead to problems caused by having more ibrutinib in the body than intended. Imbruvica should be used carefully in patients with mild or moderate liver disease, and must not be used in patients with severe liver problems.
Long-term use (>2 years)	No information from clinical trials is available to support the long-term use of Imbruvica (for more than 2 years)

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 Imbruvica can be found on Imbruvica's EPAR page.

This medicine has no additional risk minimisation measures.

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
PCYC-PMR-2060-03 In vitro studies on the	To evaluate the effect of ibrutinib	Haemorrhage (bleeding)	Planning stages	To be determined

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
effect of ibrutinib on platelet function.	on bleeding.			
PCYC-PMR-2060-04 Analysis of the risk of serious bleeding.	To study the risk of serious bleeding from clinical trials and all post-marketing sources	Haemorrhage (bleeding)	Planning stages	To be determined
PCI-32765LYM1003 A drug-drug interaction study of ibrutinib with moderate and strong CYP3A inhibitors in patients with B-cell malignancy.	To assess ibrutinib when combined with other medicines (enzymes).	Drug-drug interaction	Planning stages	To be determined
PCYC-1112-CA Yearly updates, including del17p/TP53 subgroups identified at baseline, for the randomised, multicentre, open-label trial in subjects with CLL who have failed at least 1 prior line of therapy; Assess PFS by IRC trial.	Yearly updates of trial results for disease progression and death.	Overall safety profile	Yearly updates	2nd Quarter 2015 2nd Quarter 2016 2nd Quarter 2017 4th Quarter 2017
JNJ-54179060/FK10654 Study on the inhibition potential of ibrutinib and four metabolites on OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) transport in HEK293 cell lines overexpressing this transporter.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Started	1st Quarter 2015
JNJ-54179060/FK10655 Study on the inhibition potential of ibrutinib and four metabolites on OAT3 (SLC22A8) transport in MDCK-II cell lines overexpressing this	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Started	1st Quarter 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
transporter.				
JNJ-54179060/FK10656 Study on the inhibition potential of ibrutinib and four metabolites on OAT1 (SLC22A6) and OCT2 (SLC22A2) transport in CHO cell lines overexpressing this transporter.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Started	1st Quarter 2015
JNJ-54179060/FK10657 An in vitro study on the possible BRCP (ABCG2) transport inhibition by ibrutinib and four metabolites.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Started	1st Quarter 2015
In vitro study of time-dependent inhibition by ibrutinib on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Planned	1st Quarter 2015
An in vitro inhibition experiment for reversible CYP3A inhibition by ibrutinib minimising the decline in ibrutinib concentration during incubations.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Planned	1st Quarter 2015
An in vitro study into hepatic CYP1A2 and CYP2B6 induction with the inclusion of unchanged ibrutinib recovery assessment during and at the end of the incubation.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Planned	1st Quarter 2015
PCI-32765 CLL1006 Phase 1, open-label, single-dose, multicentre, non-randomised trial in healthy subjects and subjects with hepatic	Measure the effect of liver disease on the amounts of ibrutinib in the body.	Use in patients with liver disease	Trial completed on 30 March 2014	Ongoing Planned final report submission: 4th Quarter 2014

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
impairment.				
PCI-32765 CLL1007 Thorough QT study.	To assess the effect of ibrutinib on the electrical rhythm of the heart.	Irregular heartbeat. Use in patients with significant heart disease.	Planned	Final protocol submission: 4th Quarter 2014 Final report submission: 4th Quarter 2016
PCI-1103-CA (ongoing) Open-label, extension trial in subjects with B-cell lymphoma and CLL to determine the long-term safety of ibrutinib.	Determine the long-term safety of ibrutinib.	Long-term use (>2 years)	Ongoing	Interim report 2nd Quarter 2016
PCI-32765 CAN3001 Open-label, extension study in subjects with MCL.	To assess the long-term safety of ibrutinib.	Long-term use (>2 years)	Ongoing	Interim report: 2nd Quarter 2016
PCI-32765MCL2001 Phase 2, multicentre, single-arm trial in subjects with MCL who have received ≥1 rituximab-containing regimen and progressed after receiving ≥2 cycles of bortezomib therapy.	Evaluate the response of ibrutinib compared with another medicine called bortezomib.	Overall safety profile	Ongoing	1st Quarter 2016 final
PCI-32765MCL3001 Phase 3, randomised, controlled, open-label, multicentre trial in subjects with relapsed/refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen.	Evaluate efficacy and safety of ibrutinib compared with another medicine called temsirolimus.	Overall safety profile	Ongoing	1st Quarter 2016 final
PCI-32765MCL3002 Phase 3, randomised, double-blind,	Evaluate efficacy and safety of ibrutinib.	Overall safety profile	Ongoing	3rd Quarter 2020 final

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
placebo-controlled, multicentre trial in subjects with newly diagnosed MCL with no prior therapies for MCL.				
PCYC-1117-CA Phase 2, open-label, single arm, multicentre trial in subjects with relapsed or refractory CLL with 17p deletion	Evaluate response rate and safety of ibrutinib.	Overall safety profile	Ongoing	4th Quarter 2015
PCYC-1115-CA Phase 3, randomised, multicentre, open-label study in subjects ≥65 years with treatment-naive CLL.	Evaluate the efficacy of ibrutinib compared with chlorambucil	Overall safety profile	Ongoing	4th Quarter 2016
PCI-32765CLL3001 Phase 3, randomised, multicentre, double-blind, placebo-controlled trial in subjects with relapsed or refractory CLL (excluding subjects with del17p).	Evaluate survival rates with ibrutinib.	Overall safety profile	Ongoing	3rd Quarter 2018
A clinical interaction study to evaluate the effect of proton pump inhibitors.	To assess what might happen when ibrutinib is combined with other medicines.	Drug-drug interaction	Planned	3rd Quarter 2016
A non-clinical study regarding the transgenic (Tg) mouse range-finder study.	A study in mice, to understand the safety of ibrutinib and find the most suitable doses for longer studies; to find out how the body's systems handle and get rid of ibrutinib.	Other malignancies	Planned	3rd Quarter 2015
Following the mouse range-finder study: A non-	A study in mice, to find out how likely	Other malignancies	Planned	1st Quarter

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
clinical study regarding the Tg ras H2 6 month mouse carcinogenicity study.	ibrutinib is to cause cancer-related problems.			2018
A feasibility assessment on conducting an interaction study between ibrutinib and oral contraceptives.	To assess whether ibrutinib affects the efficacy of oral contraceptive.	Drug-drug interaction	Planned	Final feasibility assessment report 1st Quarter 2015

Studies which are a condition of the marketing authorisation

As part of the marketing authorisation for Imbruvica, the company is obliged to submit yearly updates of study PCYC-1112-CA in patients with chronic lymphocytic leukaemia and the final report of another study, PCI-32765MCL3001, in patients with mantle cell lymphoma.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2014.