EMA/476566/2014

Summary of the risk management plan (RMP) for Zydelig (idelalisib)

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

Overview of disease epidemiology

Zydelig is a cancer medicine that is used to treat two types of blood cancer: chronic lymphocytic leukaemia and follicular 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 10,000 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.

Follicular lymphoma is an indolent (or slow-growing) form of another cancer of the B lymphocytes known as non-Hodgkin lymphoma. Most cases of indolent non-Hodgkin lymphoma affect people older than 60 years of age. It is also a rare disease and affects up to 4 people in 10,000. With treatment, patients can expect to live from 5 years to up to 10 years or more, depending on the extent (stage) and location of their cancer.

Summary of treatment benefits

In a main study of 220 patients with previously treated chronic lymphocytic leukaemia, Zydelig was shown to be more effective at treating the cancer than placebo (a dummy treatment) when both were given in combination with another medicine rituximab: 75% of patients taking Zydelig had an improvement in their disease compared with 15% of patients taking placebo. Zydelig was also more effective than placebo in the subgroup of patients who had a specific genetic mutation in their cancer cells that makes them unsuitable for chemo-immunotherapy.

Another main study evaluated Zydelig in patients with different lymphomas, including 72 patients with follicular lymphoma that had failed two previous treatments. Zydelig was shown to be effective, with 54% of patients with follicular lymphoma having either a complete or partial response to treatment.

Unknowns relating to treatment benefits

Zydelig has not been studied in children. Zydelig has not been studied in patients with severe liver or kidney impairment. There are only limited data on the long-term use of Zydelig.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increased liver enzyme (transaminase) levels in the blood	Increases in liver enzyme levels that occur early in the course of therapy have been observed in clinical studies. In many cases, the liver enzyme levels return to normal without any treatment. In some cases the liver enzyme levels become too high requiring treatment with Zydelig to be stopped. Increased liver enzyme levels is listed as a very common side effect (occurring in more than 1 patient in 10) in the product information for Zydelig.	It is not known how an increase in liver enzyme levels can be prevented, but when it occurs stopping Zydelig can lead to the enzyme levels returning to normal. Regular blood tests should be carried out during the first few weeks and months of therapy to detect an increase in liver enzyme levels. Treatment may be restarted at a lower dose once the levels of enzymes have improved.
Watery diarrhoea (diarrhoea/colitis)	Severe diarrhoea can occur after many months of therapy. More than 1 patient in 10 have experienced inflammation of the bowel and watery diarrhoea occurring several times a day and lasting for weeks. Watery diarrhoea is listed as a very common side effect in the product information for Zydelig	It is not known how diarrhoea can be prevented, but when it occurs it can be managed by temporarily stopping Zydelig and by treatment with anti-diarrhoeals, and/or anti-inflammatory medicines that are effective in the gastrointestinal tract. Treatment may be restarted at a lower dose once the diarrhoea has improved.
Lung inflammation (pneumonitis)	Lung inflammation has been seen in some patients receiving Zydelig but it is not known whether it is caused by Zydelig or by other concomitant cancer treatments. This lung inflammation is sometimes severe enough to require mechanical ventilation and has, very rarely, led to death.	It is not known how lung inflammation can be prevented, but when it occurs it can be treated. Patients who experience shortness of breath and cough without any signs of infection, should stop treatment and be treated with corticosteroids. Treatment can be restarted once the lung inflammation has resolved. If the lung symptoms come back, treatment with Zydelig needs to be permanently stopped.
Decreased levels of white blood cells (neutropenia)	Decreased levels of white blood cells have been seen in more than 1 patient in 10 treated with	It is not known how a decrease in white blood cell levels can be prevented, but when it occurs stopping Zydelig can lead

Risk	What is known	Preventability
	Zydelig in clinical studies. Decreased levels of white blood cells is listed as a very common side effect in the product information for Zydelig	to the white blood cells levels returning to normal. Treatment may be restarted once the levels of white blood cells have returned to normal.
Rash	Patients have experienced rash after starting treatment with Zydelig. The rash is usually a flat, red area of the skin (on the trunk and extremities) associated with occasional fever or itching. The rash was generally mild to moderate and rarely resulted in discontinuation of treatment. It typically resolved with treatment and dose interruption for severe cases.	It is not known how rash can be prevented, but when it occurs it can be treated with antihistamine and/or topical (skin) or oral steroids. In the event of severe rash, treatment must be stopped.

Important potential risks

Risk	What is known
Birth defects (including teratogenicity)	In animal studies with Zydelig harmful effects were seen on the foetus and on fertility. No human data are available. Zydelig is not recommended for use during pregnancy, and women taking the medicine should use a reliable method of contraception to avoid becoming pregnant during treatment and for 1 month after treatment. As it is not known whether Zydelig can make hormonal contraceptives less effective, women should also use a barrier method of contraception such as condoms.
Use of Zydelig with certain medicines called CYP3A inducers	Zydelig is processed in the body by CYP3A enzymes. Certain medicines can increase the activity of these enzymes. They are called CYP3A inducers and include rifampicin (used to prevent and treat tuberculosis), phenytoin and carbamazepine (used to prevent seizures) and St. John's wort (a herbal remedy used for depression and anxiety). By increasing CYP3A activity, CYP3A inducers can reduce the levels of Zydelig in the blood thereby reducing its effectiveness.
Use of Zydelig with medicines normally processed by CYP3A (called CYP3A substrates)	As Zydelig itself blocks CYP3A enzymes, it could potentially increase the effects of other medicines metabolised by the enzymes or make their side effects worse. Zydelig should be used with caution with these medicines. In particular, Zydelig should not be used concomitantly with any of the following medicinal products due to the potential for serious or life-threatening side effects: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine,

Risk	What is known
	dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam and triazolam.
Sunburn-like reactions following exposure to light (photosensitivity)	Studies in experimental models indicate that there could be a risk of photosensitivity with Zydelig. Photosensitivity effects of Zydelig in humans have not been established.
Skin cancer	Chronic lymphocytic leukaemia is associated with an increased incidence of skin cancer, which is thought to be linked to cancer's suppressing of the immune system as well as the treatment. Because Zydelig acts on the immune system, skin cancer is a potential risk. The potential for developing skin cancer with Zydelig has not yet been established.

Missing information

Risk	What is known
Drug resistance (reduction in the medicine's effectiveness)	The potential for development of drug resistance with Zydelig has not yet been established.
Tumour inducing potential (carcinogenicity)	The tumour inducing potential (carcinogenicity) of Zydelig has not yet been established.
Long-term safety	There is limited experience with prolonged use of Zydelig (over 1 year) in clinical trials. The long-term safety of Zydelig has not yet been established.
Use in patients with severe liver impairment	The safety of Zydelig is not known in patients with severely decreased liver function.
Use in patients with severe kidney impairment	There is limited information on the use of the medicine in patients with severe kidney impairment. Increases in the levels in the body of Zydelig's active substance idelalisib and its major metabolite (the substance produced when idelalisib is broken down) were minimal and not clinically meaningful in patients with severely decreased kidney function.
Use in patients with chronic active hepatitis	The safety of Zydelig is not known in patients with chronic (long-term) active hepatitis including viral hepatitis.
Use in patients undergoing immunisation (vaccination) during treatment	The safety of Zydelig is not known in patients with concomitant immunisation.

Risk	What is known
Immunological effects and auto-immunity	The effects of idelalisib on the immune system, including how it may trigger immune reactions against the body's own cells (auto-immunity), are not known.
Use in children	The safety and efficacy of Zydelig have not yet been established in children.
Use while breastfeeding	It is not known whether the ingredients in Zydelig pass into human breast milk. Breastfeeding should be discontinued during treatment with Zydelig..
Interaction with oral contraceptive	It is not known whether Zydelig interacts with oral contraceptives. Women using hormonal contraceptives should also use a barrier method to avoid becoming pregnant while taking Zydelig and for a month after stopping treatment.

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 Zydelig can be found on Zydelig'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
GS-US-312-0116	To evaluate the safety and efficacy of idelalisib in combination with rituximab in patients with relapsed chronic lymphocytic leukaemia.	Long-term safety and efficacy	Ongoing	December 2014
GS-US-312-0117	To evaluate the safety and efficacy of idelalisib in combination with rituximab in patients with relapsed chronic lymphocytic leukaemia.	Long-term safety and efficacy	Ongoing	Fourth quarter 2017
101-09	To evaluate the safety and	Long-term safety	Ongoing	December 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	efficacy of idelalisib monotherapy in patients with refractory indolent non-Hodgkin lymphoma.	and efficacy		
BP-US-313-0128 (Interventional clinical study)	To evaluate what the body does to Zydelig and the extent to which Zydelig becomes available to the body and how children tolerate Zydelig.	Safety in children	Planned	Not determined
BP-US-313-0129 (Interventional clinical study)	To evaluate safety and efficacy of Zydelig when used with standard of care multi-agent chemotherapy in children.	Safety in children	Planned	Not determined
Study BP-US-312-1616 An in vivo interaction (induction) study with oral contraceptive (PK study)	To evaluate the effect of idelalisib co-administration on the pharmacokinetics of a representative oral contraceptive.	Oral contraceptive drug-drug interaction study	Planned	February 2015 (Feasibility report and proposal for study design)
AD-312-2030 Further studies on the human enzymology of idelalisib oxidation (Nonclinical study)	To determine the role of aldehyde oxidase in the metabolism of idelalisib.	Drug-drug interactions with aldehyde oxidase	Planned	December 2014
AD-312-2029 In vitro assessment of GS-1101 as a substrate for human OATP1B1 and OATP1B3 over an extended concentration range (Nonclinical study)	To determine the OATP1B1 and OATP1B3 substrate characteristics of idelalisib.	Drug-drug interactions with transport substrates	Planned	December 2014
TX-312-2017	To evaluate carcinogenicity	Carcinogenicity	Ongoing	Second quarter

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A 2-year oral (gavage) carcinogenicity study of idelalisib in sprague dawley rats (Nonclinical study)	with idelalisib therapy.			2017
TX-312-2019 26-week oral gavage carcinogenicity and toxicokinetic study with idelalisib in RasH2 [001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic] mice (Nonclinical study)	To evaluate carcinogenicity with idelalisib therapy.	Carcinogenicity	Planned	Second quarter 2017
TX-312-2018 4-week oral dose range-finding toxicity and toxicokinetic oral gavage study with idelalisib in 001178-W (wild type) RasH2 mice (Nonclinical study)	To determine the safety of the main human metabolite GS-563117.	Safety of the main human metabolite GS-563117	Ongoing	Fourth quarter 2014
PC-312-2016 Radioligand binding assay with GS-563117 (Nonclinical study)	To determine the safety of the main human metabolite GS-563117.	Safety of the main human metabolite GS-563117	Ongoing	Fourth quarter 2014
Multiple studies Mechanistic studies on the effect of idelalisib on immune function (Nonclinical study)	To evaluate data on immunological effects and auto-immunity.	Immunological effects and auto-immunity	Planned	March 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Drug mechanism of resistance studies for CLL (samples collected from completed and ongoing studies: GS-US-312-0116, GS-US-312-0117 and GS-US-312-0119) and iNHL (Nonclinical study)	To investigate the mechanism of drug resistance with idelalisib.	Development of drug resistance	Started	December 2014 (CLL) To be determined (iNHL)

Studies which are a condition of the marketing authorisation

As part of the marketing authorisation for Zydelig, the company is obliged to submit the final reports of two ongoing studies in patients with chronic lymphocytic leukaemia (GS-US-312-0116 and GS-US-312-0117) and of another study, 101-09, in patients with indolent B-cell non-Hodgkin's lymphoma.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2014.