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Summary of the risk management plan (RMP) for Otezla (apremilast)

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

Overview of disease epidemiology

Otezla is a medicine used to treat psoriasis (an inflammatory disease causing red, scaly patches on the skin that may be itchy or painful, and can also affect the scalp and nails) and psoriatic arthritis (an inflammatory disease of the joints, usually associated with psoriasis).

Psoriasis has been reported to occur in approximately 1 to 3.5% of the population although the figure may vary somewhat with factors such as age, gender and geographic location. Psoriasis is more likely to occur in people with a family history of psoriasis or those who smoke, drink alcohol, experience stress, or who have had bacterial and viral infections.

Psoriatic arthritis commonly occurs in people with psoriasis and typically occurs between the ages of 30 and 55 years, usually several years after the development of psoriasis itself. It is equally common among men and women but slightly more common in people of white ethnicity and those who have experienced physical injuries or who have high blood pressure. It is estimated that between 20 and 420 out of every 100,000 people in the European population may have the condition.

People who have psoriatic arthritis and psoriasis can develop other medical conditions including other inflammatory conditions, heart problems, diabetes and high blood pressure. They may also be at higher risk of developing infections, liver disease, depression/anxiety or diseases of the nervous system.

Psoriasis and psoriatic arthritis are long-lasting (chronic) diseases that can require long-term treatment over decades. Psoriatic arthritis can lead to irreversible damage to joints. There is a slightly increased number of deaths among people with psoriatic arthritis compared with the general population.

Summary of treatment benefits

Otezla contains the active substance apremilast which blocks an enzyme inside cells called phosphodiesterase 4 (PDE4). PDE4 is responsible for triggering the release of messenger molecules in the immune system (the body's natural defences) involved in causing inflammation, including in psoriasis and psoriatic arthritis. By blocking the action of PDE4, apremilast reduces the symptoms of these conditions.

Otezla has been shown to be of benefit in psoriasis in two main studies involving a total of 1,257 patients with moderate to severe plaque psoriasis, in which treatment with Otezla was compared with

placebo (a dummy treatment). The main measure of effectiveness in both studies was the proportion of patients who 'responded' to treatment after 16 weeks. Response to treatment was defined as patients whose symptom scores for assessing severity and extent of psoriasis reduced by at least 75% (PASI-75). Of the patients given Otezla in these studies, 33% (168 of 562) and 29% (79 of 274) responded to treatment. This compared with 5% (15 of 282) and 6% (8 of 137) given placebo.

For psoriatic arthritis, Otezla has been compared with placebo in 3 main studies involving 1,493 patients with active disease despite prior treatment. Patients who were already taking other so-called 'small-molecule DMARDs' such as the medicine methotrexate continued this treatment during the study. The main measure of effectiveness was a 20% improvement in a score measuring symptoms such as tender and swollen joints (ACR-20) after 16 weeks of treatment, and this was achieved in between 32 and 41% of patients given the approved dose of Otezla in the three studies, compared with 18 to 19% of those given placebo. Benefit was seen both in patients taking Otezla alone and those also taking other DMARDs.

For both psoriasis and psoriatic arthritis there was evidence of maintained benefit when treatment was extended (to 32 and 52 weeks respectively).

Unknowns relating to treatment benefits

Patients in the studies used to approve Otezla were mostly white. There is no evidence that results would be different in non-white patients.

Patients with moderate/severe kidney disorders, liver disorders, children and pregnant or breastfeeding patients were excluded from clinical trials. Therefore, there is no information on safety or effectiveness of Otezla for these patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity)	Allergic reactions are uncommon with Otezla (seen in less than 1 patient in 100).	As allergic reactions can be serious and require hospitalisation, it is important that both the doctor and patient are aware that such reactions can occur. Patients with an allergy to Otezla's active substance, apremilast, or any other ingredients of the medicine should not take Otezla.
Effect of other medicines on Otezla (Pharmacokinetic interaction with strong CYP3A4 inducers)	Some other medicines (called 'strong CYP3A4 inducers') can increase the breakdown of apremilast in the body, and therefore if taken together with Otezla may make the medicine less effective. Such medicines include in particular rifampicin, which is used to treat tuberculosis and related infections, as well as some medicines used mainly for epilepsy or fits (carbamazepine,	Patients should be monitored for the use of other medicines that may have an effect on Otezla, in particular rifampicin. Patients should tell their doctor or pharmacist if they are taking or plan to take other medicines.

Risk	What is known	Preventability
	phenobarbital and phenytoin) and St John's wort, a herbal medicine for depression.	
Weight decrease in patients with body mass index (BMI) below 20 kg/m^2	Weight loss is associated with the class of active substances to which apremilast belongs, and has been seen uncommonly (in less than 1 patient in 100) in patients treated with Otezla. Therefore, it is considered a risk to underweight patients who are treated with the medicine.	Body weight should be monitored in patients who are underweight at the start of treatment. In the event of unexplained and clinically significant weight loss, these patients should be evaluated by a doctor and stopping treatment should be considered.
Depression	In studies, depression has been reported in around 1 patient in 100 being treated with Otezla.	Patients should be monitored for the early signs and symptoms of depression.

Important potential risks

Risk	What is known
Inflammation of blood vessels (Vasculitis)	Inflammation of blood vessels, known as vasculitis, is considered a potential risk of Otezla treatment because it caused inflammation of the tissue surrounding blood vessels in animal studies. However, this inflammation usually stopped even when Otezla treatment was continued. In clinical studies in patients with psoriatic arthritis, vasculitis was a rare side effect, occurring in fewer than 1 in 1,000 people but more than 1 in 10,000. No patients in the studies of psoriasis developed vasculitis.
Risk of triggering suicide (suicidal thoughts)	Risk of triggering suicide is considered a potential risk of Otezla treatment because suicidal thoughts and behaviour have occurred rarely (in fewer than 1 person in 1,000) in patients taking roflumilast, a medicine belonging to the same class of active substances as the apremilast in Otezla.
Tumours (Malignancies)	Some patients taking Otezla in studies have developed cancer and so this is considered a potential risk. However, many of these patients had risk factors such as a family history, history of prior skin cancer, or exposure to substances known to be associated with increased risk of cancer. In addition, most of these events were diagnosed in the first 6 months of starting treatment with the medicine, and since cancers usually take some time to develop it is unlikely that the occurrence of the malignancies is connected with Otezla.
Nervousness and anxiety	No specific risk of increased nervousness or anxiety has been reported with Otezla. Nervousness or anxiety is considered a potential risk of Otezla treatment because nervousness or anxiety have occurred rarely (in less than 1 person in 1,000) in patients taking roflumilast, a medicine belonging to the same class of active substances as the apremilast in Otezla. As in general practice, patients who have signs or symptoms of nervousness or anxiety may

Risk	What is known
	require additional evaluation and treatment.
Serious infections	Because Otezla affects part of the immune system, there is a potential risk that it could reduce the ability of the body to fight off infections. However, during the clinical studies, the frequency of infections was comparable between patients given a dummy treatment and those treated with Otezla. The frequency of infections did not increase when patients continued treatment with Otezla for a longer time.
Major heart problems (major adverse cardiac events [MACE] and tachyarrhythmia)	The occurrence of major heart problems and rapid, irregular heartbeats (tachyarrhythmias) during the clinical studies was slightly higher in patients given Otezla than those given a dummy treatment, although this could have been due to chance; the rate of major heart problems is higher in patients with psoriasis and psoriatic arthritis than in the normal population.
Effects on the developing child if used during pregnancy (Prenatal embryo-foetal loss and delayed foetal development [reduced ossification and foetal weight] in pregnant women exposed to apremilast)	There are no studies of Otezla in pregnant women, and it is not known whether Otezla will harm the unborn baby. However, it is considered a potential risk because studies in monkeys showed there is an increased risk of miscarriage or death of the unborn offspring in animals given more than the dose of Otezla that would be taken by patients. Otezla must not be used if patients are pregnant or suspect they may be pregnant. Before treatment with Otezla can start, pregnancy should be ruled out. Women should not become pregnant while taking this medicine and should use an effective method of contraception to prevent pregnancy during treatment.

Missing information

Risk	What is known
Use in children younger than 18 years (Paediatric Use)	Children below 18 years of age have not been included in Otezla studies. Therefore, it is not known whether Otezla is safe and effective in children.
Patients with moderate and severe reduction in kidney function (Renal impairment)	The safety of Otezla in patients with mildly reduced kidney function is similar to its safety in patients with normal kidney function. However, the safety of Otezla in patients with more severe kidney impairment has not been studied. Moderate kidney impairment does not affect how Otezla is broken down by the body; however, severe kidney impairment does affect how it is broken down by the body. The dose needs to be adjusted in patients with severe kidney impairment. Before taking Otezla, patients must talk to their doctor if they have kidney problems.
Safety and effectiveness with use	The safety and effectiveness of Otezla when used for a long time (over 1 year)

Risk	What is known
over a long time (Long-term safety; Limited data on long-term efficacy)	is not yet known.
Patients with moderate and severe reduction in liver function (Hepatic impairment)	The safety of Otezla in patients with liver impairment has not been studied. However, moderate or severe liver impairment does not affect how Otezla's active substance, apremilast, is broken down by the body. Therefore the dose does not need to be adjusted in patients with liver impairment.
Use in patients of different racial origin	The safety of Otezla in patients of different racial origins (non-white) has not been studied.
Live vaccination	Although the use of live vaccines was not allowed during the clinical studies, a few patients received them by mistake. The side effects reported were similar between patients who were vaccinated and those who did not receive any live vaccine.
Effect of other medicines on the breakdown product of apremilast (Potential pharmacokinetic interactions of apremilast metabolite M12)	The active substance in Otezla, apremilast, is broken down in the body into various other substances (metabolites) including in particular one called M12. It is not yet known if this metabolite may affect or be affected by other medicines.

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 Otezla can be found on Otezla'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

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Up to 5-year treatment duration of Phase 3 studies (CC-10004-PSA-002, -003, -004, -005 and CC-10004-PSOR-008, -009) to collect long-term data	To collect long-term data.	Malignancies. Long-term safety.	Ongoing.	Clinical study reports (CSRs) anticipated quarter (Q)4 2017.
Up to 2-year treatment duration of Phase 3 study (CC-10004-PSOR-010) to collect long-term data	To collect long-term data.	Malignancies. Long-term safety. Limited data on long-term efficacy.	Ongoing.	Interim CSR anticipated Q2 2015. Final CSR anticipated Q3 2016.
Apremilast Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy	To monitor planned or unplanned pregnancies exposed to apremilast.	Effects on the developing child if used in pregnancy.	Ongoing.	Final CSR anticipated Jun 2022
Disease Registry in the EU for psoriatic arthritis (PsA) and psoriasis (PsoBest, BSRBR)	To collect long-term data in real world setting.	Hypersensitivity. Depression. Vasculitis. Risk of triggering suicide. Malignancies. Nervousness and anxiety. Serious infections. MACE and tachyarrhythmia. Long-term safety.	Planned.	The final protocol for the PsoBest registry will be provided by 30 Jun 2015 and the registry will start 01 Jul 2015. The final protocol for the British Society for Rheumatology Biologics Register (BSRBR) registry will be provided by 31 Dec 2015 and the registry will commence in Jan 2016.
Clinical Practice Research Database (CPRD;	To collect long-term data in real	Hypersensitivity. Depression.	Planned.	Analysis of the CPRD data at Years 1, 3 and 5,

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
UK) data analysis for PsA and psoriasis	world setting.	Vasculitis. Risk of triggering suicide. Malignancies. Nervousness and anxiety. Serious infections. MACE and tachyarrhythmia. Long-term safety.		starting from the date of first commercial availability in the UK. A protocol will be submitted for review by 30 Jun 2015. First analysis will be conducted 1 year from the date of first commercial availability in the UK.
In vitro studies (CC-10004-DMPK-1965 and CC-10004-DMPK-1966)	To evaluate the potential pharmacokinetic interactions of apremilast metabolite M12.	Potential pharmacokinetic interactions of apremilast metabolite M12.	Ongoing.	Final study reports will be submitted Q1 2015.

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation for Otezla.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 12-2014.