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Summary of the risk management plan (RMP) for Neuraceq [florbetaben (^{18}F)]

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

Overview of disease epidemiology

Dementia is a frequent and disabling disease in the older population. The most common form of dementia is Alzheimer's disease (AD); other forms of dementia are vascular dementia, mixed types, Lewy body dementia, fronto-temporal dementia and others.

The cause and progression of AD are not well understood. Less than 5% of Alzheimer cases are caused by specific genetic changes that indicate that a person will develop the disease. Research indicates that AD is associated with the formation of deposit of protein (beta-amyloid) in the brain. These deposits, known as plaques, cause damage to brain cells and interfere with cell-to-cell communication. The collection of beta-amyloid on the outside of brain cells is thought to be a prime cause of brain cell death in patients with AD. Furthermore, brain cells depend on an internal support and transport system to carry nutrients and other essential materials throughout their long extensions. This system requires the normal structure and functioning of a protein called tau. In AD, threads of tau protein twist into abnormal tangles inside brain cells, leading to failure of the transport system. This failure is also strongly implicated in the decline and death of brain cells. Thus AD is characterized by extensive brain shrinkage that gets worse over time. The most important risk factors for AD are old age and a positive family history for the disease.

Summary of treatment benefits

Florbetaben (^{18}F) is a radioactive 'diagnostic imaging agent' used to determine if beta-amyloid plaques are present in the brain. Presence of beta-amyloid plaques has been found in subjects with AD. Knowing if deposits of this protein are present in the brain can help a doctor in diagnosing dementia.

Florbetaben (^{18}F) works by attaching to beta-amyloid, if it is present in the brain. When attached to florbetaben, beta-amyloid can be detected during 'positron emission tomography' (PET) brain scans.

Florbetaben (^{18}F) was used in 31 patients while they were alive, and their PET scans were compared with an autopsy of their brain after death. The uptake of florbetaben (^{18}F) in the brain was analysed by PET scanning and the resulting images were compared with the presence of beta-amyloid plaques in the brain during autopsy. The presence or absence of beta-amyloid in the brain was assessed with a high sensitivity and specificity. The results showed that PET scans with florbetaben (^{18}F) can detect beta-amyloid plaques in the brain, and can help in the diagnosis of dementia.

Unknowns relating to treatment benefits

The usefulness of florbetaben (^{18}F) in patients with structural abnormalities in their brain such as brain trauma or tumours has not been studied; however, in practice an evaluation for AD in such patients would not be a priority. Given the fact that beta-amyloid deposition generally occurs in many regions and in both sides of the brain, a structural disruption would in most cases not affect the assessment of the PET scan. There may be cases in which the grey-white matter border or other brain structural 'landmarks' are altered in such a way that the PET scan analysis is not possible. This is felt to be a potential confounder in a small number of cases.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Reactions around point of injection (local tolerance)	As with any injected medication, reactions around the point of injection may occur (e.g. injection site pain or injection site irritation). These reactions are generally mild and do not require any form of treatment. Older patients are at a higher risk because of their fragile veins.	Care should be taken to avoid any of the medication from being injected outside of the vein.
Risk due to contact with radiation (carcinogenic and hereditary risk)	Contact with radiation can cause cancer or the development of hereditary DNA changes. This risk increases with the quantity of radiation. The amount of radiation with florbetaben (^{18}F) is similar to other examinations involving nuclear medicine and the potential radiation risk associated with the use of florbetaben (^{18}F) is in the acceptable limits.	The lowest possible dose of radiation should be used.

Important potential risks

Risk	What is known
Reactions to the alcohol content of the injection (reactions to ethanol content of formulation)	Alcohol is used in many prescription and non-prescription medicines, to help make the medicine more soluble. It can also be used as a preservative. The maximum volume of alcohol in an injection of florbetaben (^{18}F) is the same as 30 mL of beer or 12 mL of wine. Although adverse reactions to this small amount of alcohol are rather unlikely, patients suffering from alcoholism, liver disease or epilepsy are at a higher risk for adverse reactions. Patients being treated with an alcohol deterrent such as disulfiram should discontinue this medication before receiving florbetaben (^{18}F).

Injection of the medicine outside of a vein (extravasation)	If a large proportion of the medicine is injected into the tissue around the vein, this could cause a wound because of the radiation, alcohol and another substance (macrogol) that is in the injection. Careful injection of florbetaben (^{18}F), making sure that the medicine is being injected into the vein, can reduce the possibility of this happening. In order to minimise the risk of extravasation, the patency of the vein (its being open or unobstructed) must be ensured by a test injection of normal saline solution prior to injection of florbetaben (^{18}F). Additionally, a slow injection into a large arm vein is recommended, followed by a saline flush of approximately 10 mL.
Hypersensitivity (allergy)	In patients who are allergic to florbetaben (^{18}F) (or any of the excipients) hypersensitivity (allergic) reactions may occur after injection of the medicine. Such a reaction may even evolve to an anaphylactic reaction (severe allergic reaction), which can be life-threatening.
PET scan interpretation errors	Interpretation errors by the physicians who read the acquired images may lead to subsequent inappropriate treatment strategies for their patients.
Off-label use	Florbetaben (^{18}F) is not recommended for use other than in older patients being investigated for Alzheimer's disease. Use in other populations was not sufficiently investigated.

Missing information

Risk	**What is known**
Safety in patients with reduced kidney function	The pharmacokinetics of florbetaben (^{18}F) in patients with reduced kidney function has not been characterized. Data will be collected and evaluated in the frame of a post-authorisation safety study (PAS-2) and during evaluation of an ongoing phase III trial.
Safety in patients with reduced liver function	The pharmacokinetics of florbetaben (^{18}F) in patients with reduced liver function has not been characterized. Consequences of florbetaben (^{18}F) use in patients with severely reduced liver function are not known. Therefore florbetaben (^{18}F) is not recommended in these patients. Data will be collected and evaluated in the frame of a post-authorisation safety study (PAS-2) and during evaluation of an ongoing phase III trial.
Drug-drug interaction (disulfiram)	Drug-drug interactions studies have not been conducted. Due to its alcohol content, florbetaben (^{18}F) may interfere with other medicines such as disulfiram used for the treatment of patients with alcoholism, but there are no data indicating that such an interaction exists. The effect of potential drug-drug interaction with disulfiram on effectiveness and safety will be monitored in a post-authorisation safety study (PAS-2).

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 Neuraceq can be found on Neuraceq'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 in Neuraceq'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:

PET scan interpretation errors

Risk minimisation measures	**Healthcare professionals' educational programme**
Objective and rationale	Educational material and training for PET scan readers to avoid false interpretation of images and subsequent inappropriate treatment of patients.
Description	Educational material, training, assessment of the results of the PET scan reader's training exercise.

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**
Post-authorisation safety study (PAS-1)	To investigate the effectiveness of educational material for PET scan readers and the quality of trained reading; examine precision of PIL reading	PET scan interpretation errors Labelling (quality of special warnings and precautions for use)	Planned first draft of study protocol submitted with revised RMP version 1.2 Nov. 2013 Planned start of study: Q1 / 2015	Interim report planned for Q1 / 2016. Final study report planned for Q1 / 2018

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Ongoing phase III trial (14595)	Validation of PET imaging method Extension of safety profile	Rare adverse drug reactions Risks in specific subgroups of patients (including patients with reduced liver or kidney function)	Ongoing (start of trial: 2009) Planned study termination: end of 2013	Final study report planned for end of 2014
Post-authorisation safety study (PAS-2)	Extension of safety profile Use of florbetaben (^{18}F) including off-label use	Rare adverse drug reactions Risks in specific subgroups of patients (including patients with reduced liver or kidney function)	Planned; first draft of study protocol submitted with revised RMP version 1.2 Nov. 2013 Planned start of study: Q3 / 2014	Interim reports planned for Q1 / 2015, 2016, 2017 and 2018. Final study report planned for Q1 / 2020

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 02-2014.