Part VI: Summary of the risk management plan

Summary of risk management plan for Neuraceq (florbetaben (^{18}F))

This is a summary of the risk management plan (RMP) for Neuraceq. The RMP details important risks of Neuraceq, how these risks can be minimised, and how more information will be obtained about Neuraceq's risks and uncertainties (missing information).

Neuraceq's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Neuraceq should be used.

This summary of the RMP for Neuraceq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Neuraceq's RMP.

I. The medicine and what it is used for

Neuraceq is authorised for Positron Emission Tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. Neuraceq should be used in conjunction with a clinical evaluation. (see SmPC for the full indication). It contains florbetaben (^{18}F) as the active substance and it is given by intravenous injection.

Further information about the evaluation of Neuraceq's benefits can be found in Neuraceq's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002553/human_med_001716.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Neuraceq, together with measures to minimise such risks and the proposed studies for learning more about Neuraceq's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Neuraceq, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Neuraceq is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Neuraceq are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Neuraceq. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Injection site pain Injection site irritation
Important potential risks	Reactions due to the ethanol content of the formulation Injection site extravasation Hypersensitivity PET scan interpretation errors Off-label use
Missing information	Safety in patients with impaired hepatic function Drug-drug interaction (interaction with disulfiram)

II.B Summary of important risks

Injection site pain	
Evidence for linking the risk to the medicine	Company sponsored florbetaben (18F) phase I-IV studies, ICSRs
Risk factors and risk groups	As with any injected medication, local injection site reaction may occur and care should be taken to avoid any possible extravasation. Patients with fragile veins such as the elderly are at an increased risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 4.8 • PL section 4

Injection site irritation	
Evidence for linking the risk to the medicine	Company sponsored florbetaben (18F) phase I-IV studies, ICSRs
Risk factors and risk groups	As with any injected medication, local injection site reaction may occur and care should be taken to avoid any possible extravasation. Patients with fragile veins such as the elderly are at an increased risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 4.8 • PL section 4

Potential reactions due to the ethanol content	
Evidence for linking the risk to the medicine	Martindale – The complete drug reference
Risk factors and risk groups	Alcohol abusers. Those treated with an alcohol deterrent such as disulfiram may present symptoms such as flushing, nausea and vomiting.
Risk minimisation measures	Routine risk minimization measures: • SmPC section 4.4 • PL section 2

Injection site extravasation	
Evidence for linking the risk to the medicine	Castronovo FP Jr et al. Dosimetric consequences of radiopharmaceutical infilitrations. Investigative Radiology. 1994 Jan; 29(1):59-64. Meeting of the Advisory Committee on the Medical Use of Isotopes – United States Nuclear Regulatory Commission (NRC) Dec. 2008.
Risk factors and risk groups	As with any other injected drug risk factors include: • Patients with fragile veins, such as the elderly and patients previously treated with sclerosing or irritating drugs, • Patients unable to communication to the nurse about the pain of extravasation Elderly, debilitated patients with diabetes or general vascular disease.
Risk minimisation measures	Routine risk minimization measures: • SmPC section 4.2 and 12

Hypersensitivity	
Evidence for linking the risk to the medicine	Textbook knowledge
Risk factors and risk groups	Patients who are hypersensitive/allergic towards florbetaben (^{18}F) or any of the excipients. Patients with known hypersensitivity towards other drugs.
Risk minimisation measures	Routine risk minimization measures: • SmPC section 4.3 • PL section 2
Additional pharmacovigilance activities	PASS: Usage pattern and safety profile of Neuraceq (FBB-01_03_13) See section II.C of this summary for an overview of the post-authorization development plan.

PET scan interpretation errors	
Evidence for linking the risk to the medicine	Study 14595-Report A0002 and Study FBB_01_01_13-Report A0001
Risk factors and risk groups	Patients with brain abnormalities; motion artefacts.
Risk minimisation measures	Routine risk minimization measures: • SmPC sections 4.1, 4.2, 4.4 and 5.1 Additional risk minimization measures: • Training of PET scan readers with educational material

Off-label use	
Evidence for linking the risk to the medicine	Lott IT, Neurological phenotypes for Down syndrome across the life span. Prog Brain Res. 2012; 197: 101–121. Matías-Guiu JA, Cabrera-Martín MN, Matías-Guiu J, Oreja-Guevara C, Riola-Parada C, Moreno-Ramos T, Arrazola J, Carreras JL. Amyloid PET imaging in multiple sclerosis: an (18)F-florbetaben study. BMC Neurol. 2015 Nov 25;15:243. Turnera RS, Chadwicka M, Hortona WA, Simonb GL, Jiangc X, Esposito G. An individual with human immunodeficiency virus, dementia, and central nervous system amyloid deposition. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 4 (2016) 1-5. Mollee P, Law WP, Wang WYS, Moore PT, Ng ACT. Cardiac amyloid imaging with 18F-florbetaben positron emission tomography: A pilot study. PO-182, 15th International Myeloma Workshop, Sep 23-26, 2015.
Risk factors and risk groups	Patients with Down's syndrome, MS, cardiac amyloidosis or HAND.
Risk minimisation measures	Routine risk minimization measures: • SmPC section 4.1 • PL section 2
Additional pharmacovigilance activities	PASS: Usage pattern and safety profile of Neuraceq (FBB-01_03_13) See section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Neuraceq.

II.C.2 Other studies in post-authorisation development plan

- Usage Pattern and safety profile of Neuraceq™ (non-interventional study for Neuraceq™ in Europe)

  Purpose of the study: This is a category 3 PASS with the objective to evaluate the usage pattern of Neuraceq in clinical practice including off-label use and to extend the safety profile.

  The safety concerns addressed with this study are “off-label use” and “hypersensitivity”.