Annex I

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for edotreotide, the scientific conclusions of CHMP are as follows:

Considering the available data from the literature on misinterpretation of PET imaging due to uptake of 68-Gallium edotreotide by splenosis and accessory intrapancreatic spleen, the PRAC considers a causal relationship with edotreotide is at least a reasonable possibility, in view of a plausible mechanism of action. The PRAC concluded that the product information of products containing edotreotide should be amended accordingly.

In view of available data from the literature on the potential for misinterpretation of PET imaging due to uptake of 68-Gallium labelled somatostatin analogues by reactive lymph nodes following vaccination including cases with a close temporal relationship to receipt of COVID-19 vaccination, the PRAC concluded that the product information of products containing edotreotide should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for edotreotide the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing edotreotide is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Summary of Product Characteristics (new text **underlined and in bold**, deleted text ~~strike through~~)

- Section 4.4

A warning should be revised as follows:

~~Interpretation of gallium (68Ga) edotreotide images and limitations of use~~

Errors of interpretation of gallium (68Ga) edotreotide images

PET images with gallium (68Ga) edotreotide reflect the presence of somatostatin receptors in the tissues. The organs with high physiological uptake of gallium (68Ga) edotreotide include spleen, kidneys, liver, pituitary gland, thyroid gland and adrenals. High physiological uptake of gallium (68Ga) edotreotide by the pancreas uncinated process can also be observed.

~~In GEP-NET, a more intense gallium (68Ga) edotreotide uptake than normal background is a consistent finding. However, lesions of GEP-NET not expressing sufficient density of somatostatin receptors cannot be visualised with gallium (68Ga) edotreotide. PET images with gallium (68Ga) edotreotide should be interpreted visually, and semiquantitative measurement of gallium (68Ga) edotreotide uptake should not be used for clinical interpretation of images.~~

~~Data supporting efficacy of gallium (68Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited (see section 5.1).~~

~~In case of Cushing syndrome, a long-term exposure to endogenous hypercortisolism may down regulate somatostatin receptor expression and negatively influence the results of somatostatin receptor imaging with gallium (68Ga) edotreotide. Thus, in patients with GEP-NET and Cushing syndrome, normalisation of hypercortisolism should be suggested before performing PET with gallium (68Ga) edotreotide.~~

An increased uptake of gallium (68Ga) edotreotide is not specific for GEP-NET. **Healthcare professionals should be aware that further imaging or histological and/or other relevant investigations may be required to establish the diagnosis.**

~~Positive results require evaluating the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. As an example, an increase in somatostatin receptor density can also occur in the following pathological conditions: subacute inflammations (areas of lymphocyte concentrations), thyroid diseases (e.g. thyroid autonomy and Hashimoto's disease), tumours of the pituitary gland, neoplasms of the lungs (small-cell carcinoma), meningiomas, mammary carcinomas, lymphoproliferative disease (e.g. Hodgkin's disease and non-Hodgkin lymphomas) and tumours arising from tissue embryologically derived from the neural crest (e.g. paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas).~~

~~Spleen disorders (e.g. splenectomy, splenosis and accessory intrapancreatic spleen) should also be considered as a relevant factor when reporting the outcome of somatostatin receptor targeted diagnostics.~~ Due to physiological uptake of gallium (68Ga) edotreotide, splenosis and accessory intrapancreatic spleen may be incidentally detected **with somatostatin receptor targeted diagnostics. Cases in which such uptake has been** ~~could be~~ misdiagnosed as neuroendocrine tumours, **leading to unnecessary intervention, have been** reported. **Spleen disorders (e.g. splenectomy, splenosis and accessory intrapancreatic spleen) should therefore be considered as a relevant factor when reporting the outcome of somatostatin receptor targeted diagnostics.**

Positive results also require evaluating the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. As an example, an increase in somatostatin receptor density can also occur in the following pathological conditions: subacute inflammations (areas of lymphocyte concentrations, including reactive lymph nodes, for example following vaccination), thyroid diseases (e.g. thyroid autonomy and Hashimoto's disease), tumours of the pituitary gland, neoplasms of the lungs (small-cell carcinoma), meningiomas, mammary carcinomas, lymphoproliferative disease (e.g. Hodgkin's disease and non-Hodgkin lymphomas) and tumours arising from tissue embryologically derived from the neural crest (e.g. paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas).

In case of Cushing syndrome, a long-term exposure to endogenous hypercortisolism may down regulate somatostatin receptor expression and negatively influence the results of somatostatin receptor imaging with gallium (68Ga) edotreotide. Thus, in patients with GEP-NET and Cushing syndrome, normalisation of hypercortisolism should be suggested before performing PET with gallium (68Ga) edotreotide.

Limitations of gallium (68Ga) edotreotide imagesing

In GEP-NET, a more intense gallium (68Ga) edotreotide uptake than normal background is a consistent finding. However, lesions of GEP-NET not expressing sufficient density of somatostatin receptors cannot be visualised with gallium (68Ga) edotreotide. PET images with gallium (68Ga) edotreotide should be interpreted visually, and semiquantitative measurement of gallium (68Ga) edotreotide uptake should not be used for clinical interpretation of images.

Data supporting efficacy of gallium (68Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited (see section 5.1).

- Section 4.8

Under Description of selected adverse reactions:

~~*~~Cases in which physiological uptake of gallium (68Ga) edotreotide by splenic tissue has been misdiagnosed as neuroendocrine tumour, leading to unnecessary intervention, have been reported (see section 4.4).

Amendments to be included in the relevant sections of the Package Leaflet (new text **underlined and in bold**, deleted text ~~strike through~~)

- PIL Section 2

Talk to your nuclear medicine doctor before you are given SomaKit TOC

[…]

- if you have other medical conditions, such as high level of cortisol in the body (Cushing syndrome), inflammation, thyroid disease, other type of tumour (of pituitary gland, lung, brain, breast, immune system, thyroid, adrenal gland or others) or disease of the spleen (including previous trauma or surgery involving the spleen). Such conditions may **be visible and** affect the interpretation of the images. **Your doctor may therefore perform additional scans and tests to confirm the findings on Gallium (68Ga) edotreotide imaging.**

- **if you have been recently vaccinated. Enlarged lymph nodes due to vaccination may become visible during gallium (68Ga) edotreotide imaging**;

[…]

- PIL Section 4

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The spleen is an organ located in the abdomen (belly). Some people are born with an extra spleen (an accessory spleen). Extra spleen tissue may also be found in the abdomen following surgery or trauma to the spleen (this is known as splenosis). Gallium (68Ga) edotreotide may make an accessory spleen or splenosis visible during medical imaging. There have been reports where this has been mistaken for a tumour. Your doctor may therefore perform additional scans and tests to confirm the findings on Gallium (68Ga) edotreotide imaging (see section 2).