19 September 2013
EMA/528960/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Core SmPC and package leaflet for technetium (^{99m}Tc) sestamibi (EMA/CHMP/448591/2012)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	CIS bio international
2	Dr James Ballinger, Chief Radiopharmaceutical Scientist, Guy's and St Thomas' Hospital, London, UK
3	Mallinckrodt Medical B.V.

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	**In all templates concerning section 4.6** Fertility, pregnancy and lactation The use of drugs especially radionuclides being damageable for the capacity to have children in the future and not for the children already born, the term of **fecundity** (*fertilité* in French) seems to be more appropriate than fertility (*fécondité* in French).	The terminology is from the directive and thus we should not deviate from the regulation.
	In all templates, in section 4.6,the subtitle is not consistent with the title "Fertility, pregnancy and lactation" ~~Breastfeeding~~lactation	The subheadings in the SmPC templates can deviate from the directive. The subtitles have been agreed by the QRD subgroup.
	In all templates concerning radiopharmaceuticals, in section 6.6, the term "etc" could be replaced by "biological fluids" standing for blood (bleeding or periods), sweat…. "The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting~~ etc~~ or any other biological fluids. Radiation protection precautions in accordance with national regulations must therefore be taken."	Accepted. Will take it into consideration at the next revision of the core SmPC.
2	This is a general comment which applies to all SPCs. I disagree with the EMA policy that the quantity of only the active ingredient is stated in the SPC. With radiopharmaceuticals it is essential for the user to know the quantity of reducing agent (usually stannous chloride) as well, since this can affect product stability	

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	and sensitivity to the quality of the pertechnetate used in reconstitution.	
	With respect to sestamibi, I think this draft is correct in NOT stating whether or not there is metabolism of the product as this issue is not resolved. Some of the older SPCs still state that there is no metabolism.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
SmPC section 2 Line 11	1	Comment: missing text regarding the content of sodium. Proposed change (if any): Excipient(s) with known effect: sodium . Each vial contains *[Content : product specific]* mg of sodium.	Not accepted. This proposal should be optional as it only applies for products with sodium above the threshold according to the excipient guideline. There is a sodium free statement in section 4.4. This statement should be used on a case by case basis and thus it may become confusing to list all possible options.
SmPC section 4.1 Lines 26-27	1	Comment: The information about population is based on a misinterpretation of the core SmPC. The SmPC should be in line with the Guideline on the SmPC*. Only restrictions to the patient population should be indicated here. For this product there are no restrictions for specific age groups, therefore information about population is not needed. **" When appropriate it should define the target population especially when restrictions to the patient populations apply."* Proposed change (if any): "This medicinal product is for diagnostic use only. ~~This is indicated for adults. For paediatric population see section 4.2.~~ After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the solution of technetium (^{99m}Tc) sestamibi obtained is indicated for:"	Not accepted. According to the latest SmPC guideline, target patient population should be included in the indication.
SmPC section 4.1	1	Comment: the term Scintimammography does not seem	Not accepted. This term is used in the Breast

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 36		correct. Proposed change (if any): **"~~Scinti-mammography~~ Mammoscintigraphy for the detection of suspected breast cancer"**	Scintigraphy Procedure Guideline for Tumour Imaging.
SmPC section 4.2 Line 25	1	Comment: According to the Guideline on CoreSmPC (2009), "in case of restricted medical prescription, this section should be started by specifying the conditions." Proposed change (if any): "This medicinal product is for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel."	Question sent to the SmPC advisory group, if this is a special case.
SmPC section 4.2 Line 47	1	Comment: According to the CoreSmPC for Radiopharmaceuticals, the *statement that "other activities may be justifiable"* should be put in this subsection. Moreover the remarks about variation of posology concerns all the indications, therefore they should be stated at the top of the subsection (line 47), otherwise it could suggest they report to the indication on parathyroid only Therefore the relevant text has been moved from lines 82-83 to 48. Proposed change (if any): Posology *Adults and elderly population* Posology may vary depending on gamma camera characteristics and reconstruction modalities The injection of	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		activities greater than local DRLs (Diagnostic Reference Levels) should be justified. The suggested activity range for intravenous administration to an adult patient of average weight (70 kg) is for:	
SmPC section 4.2 Line 48	1	Comment: replacement of “suggested “ by “recommended” Proposed change (if any): “The ~~suggested~~ recommended activity range for intravenous administration to an adult patient of average weight (70 kg) is for:”	Accepted.
SmPC section 4.2 Line 74	1	Comment: non consistent with the posology stated in the current approved SPCs is : *Assessment of global ventricular function:* 600-800 MBq injected as a bolus. Proposed change (if any): “~~700-900~~ 600-800 MBq injected as a bolus.”	Accepted.
SmPC section 4.1 Line 77	1	Comment: the term Scintimammography does not seem correct. Proposed change (if any): ~~Scintimammography~~ Mammoscintigraphy 700 - 1000 MBq injected as a bolus usually in the arm opposite to the lesion.	Not accepted. This term is used in the Breast Scintigraphy Procedure Guideline for Tumour Imaging.
SmPC section 4.2 Lines 82-84	1	Comment: The remarks about variation of posology concerns all the indications, therefore they should be stated at the top of the subsection (line 47), otherwise it could suggest they report to the indication on parathyroid only. The word “**between**”and the second range given should be deleted.	Not accepted. Depending on the camera, the typical activity range is from 500-700. the 2009 EANM recommendation on parathyroid imaging cites this range as "Typical administered activity (MBq)" which in itself obvioulsy reflects the practice of Nuclear

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): .Localisation of hyperfunctioning parathyroid tissue 200 - 700 MBq injected as a bolus. The typical activity is ~~between~~ 600 MBq ~~(500-700 MBq)~~. ~~Posology may vary depending on gamma camera characteristics and reconstruction modalities.~~ ~~The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.~~	Medicine in Europe. Later in this guideline it is stated that "The average activity of technetium (99mTc) sestamibi is 600 MBq (500-700 MBq) injected intravenously" which seems to cover a more reasonable span of activities. Anabel Cortés Blanco: Our last revision version "The typical activity is between 500-700 MBq."
SmPC section 4.2 Line 86	1	Comment: The current sentence should be replaced by the standard sentence of the CoreSPC for Radiopharmaceuticals. Proposed change (if any): *Renal impairment* ~~In case of renal impairment, exposure to ionising radiation can be increased. This must be taken into account when calculating the activity to be administered.~~ Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.	Accepted.
SmPC section 4.2 Lines 98 + 100	1	Comment: - The origin and the date of data provided should be given, the date of the EANM card should be specified. - Redundancy in the sentence should be deleted. Proposed change (if any): "~~The activities to be administered to children and adolescents may be calculated according~~ According to the recommendations of the European Association of Nuclear	Not accepted. The section on paediatric population has been revised and thus the comment no longer applies.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Medicine ~~(EANM)~~ paediatric dosage card (EANM-May 2008); the activity administered to children and to….”	
SmPC section 4.2 Lines 105-109	1	Comment: The posology is not defined in a very clearly understandable way. Proposed change (if any): *Paediatric population* …..~~The activities to be administered to children and adolescents may be calculated according~~ According to the recommendations of the European Association of Nuclear Medicine ~~(EANM)~~ paediatric dosage card(EANM-May 2008); the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below as follows :. ~~A[MBq]Administered = Baseline Activity X Multiple~~ **Cancer seeking agent** Activity to be administered [MBq] = 63 MBq x Multiple (Table 1) **Two-day cardiac imaging protocol at rest and stress (minimum and maximum baselines respectively)** Activity to be administered [MBq] = 42 or 63 MBq x Multiple (Table 1) **One-day cardiac imaging protocol at rest** Activity to be administered [MBq] = 28 MBq x Multiple (Table 1) **One-day cardiac imaging protocol at stress**	Not accepted. The section on paediatric population has been revised and thus the comment no longer applies.

<table>
<tr><th>Line number(s) of the relevant text</th><th>Stakeholder number</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>Activity to be administered [MBq] = 84 MBq x Multiple (Table 1)

The minimum activity for any imaging study is 80 MBq in order to obtain images of sufficient quality.

<table>
<tr><td>Weight [kg]</td><td>Multiple</td><td>Weight [kg]</td><td>Multiple</td><td>Weight [kg]</td><td>Multiple</td></tr>
<tr><td>3</td><td>1</td><td>22</td><td>5.29</td><td>42</td><td>9.14</td></tr>
<tr><td>4</td><td>1.14</td><td>24</td><td>5.71</td><td>44</td><td>9.57</td></tr>
<tr><td>6</td><td>1.71</td><td>26</td><td>6.14</td><td>46</td><td>10.00</td></tr>
<tr><td>8</td><td>2.14</td><td>28</td><td>6.43</td><td>48</td><td>10.29</td></tr>
<tr><td>10</td><td>2.71</td><td>30</td><td>6.86</td><td>50</td><td>10.71</td></tr>
<tr><td>12</td><td>3.14</td><td>32</td><td>7.29</td><td>52-54</td><td>11.29</td></tr>
<tr><td>14</td><td>3.57</td><td>34</td><td>7.72</td><td>56-58</td><td>12.00</td></tr>
<tr><td>16</td><td>4.00</td><td>36</td><td>8.00</td><td>60-62</td><td>12.71</td></tr>
<tr><td>18</td><td>4.43</td><td>38</td><td>8.43</td><td>64-66</td><td>13.43</td></tr>
<tr><td>20</td><td>4.86</td><td>40</td><td>8.86</td><td>68</td><td>14.00</td></tr>
</table>
</td><td></td></tr>
<tr><td>SPC section 4.2

Line 117</td><td>1</td><td>Comment: The current sestamibi SPCs state the following information regarding the method of administration for mammoscintigraphy. Should it be added?

Proposed change (if any):
Mammoscintigraphy
The product is administered in an arm vein contralateral to the breast with the suspected abnormality. If the disease is bilateral, the injection is ideally administered in a dorsal vein of the foot.</td><td>Accepted.</td></tr>
</table>

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
SPC section 4.2 line 146	1	Comment: For consistency with Conventional gamma camera, the subtitle Detector dedicated to breast imaging should be underlined. Proposed change : <u>Conventional gamma camera</u> The patient should then be repositioned so that the contralateral breast is pendant and a lateral image of it should be obtained. An anterior supine image may then be obtained with the patient's arms behind her head. <u>Detector dedicated to breast imaging</u> In case a detector dedicated to breast imaging is used, a relevant machine-specific protocol must be followed to obtain the best possible imaging performance.	Accepted.
SPC section 4.2 Line155_156	1	Comment: The sentence concerning the substraction technique is not very clear. And there is a lack of consistency in the activities mentioned and those recommended in the posology Proposed change (if any): <u>For the subtraction technique</u> either sodium iodide (^{123}I) or sodium pertechnetate (^{99m}Tc) can be used <u>for imaging the thyroid gland</u> since these radiopharmaceuticals are trapped by functioning thyroid tissue. This image is subtracted from the technetium (^{99m}Tc) sestamibi image, and ~~what remains~~ pathological hyperfunctioning parathyroid tissue~~.~~ <u>remains visible after subtraction</u> .	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		When sodium iodide (^{123}I) is used, 10 to 20 MBq are orally administered. Four hours after the administration, neck and thorax images ~~are~~ may be obtained. After sodium iodide (^{123}I) image acquisition, ~~185~~ 200 to ~~370~~700 MBq of technetium (^{99m}Tc) sestamibi are injected and images are acquired 10 minutes post injection in double acquisition with 2 peaks of gamma energy (140 keV for technetium (^{99m}Tc) and 159 keV for iodine (^{123}I)). When sodium pertechnetate (^{99m}Tc) is used, 40-150 MBq are injected and neck and thorax images are acquired 30 minutes later. Then ~~185~~200-~~370~~700 MBq of technetium (^{99m}Tc) sestamibi are injected and a second acquisition of images is acquired 10 minutes later. ~~If the~~ For the dual phase technique ~~is used~~, ~~370~~ 400 to ~~740~~700 MBq of technetium (^{99m}Tc) sestamibi are injected and the first neck and mediastinum image is obtained 10 minutes later. After a wash-out period of 1 to 2 hours, neck and mediastinum imaging is again performed. The planar images may be complemented by early and delayed SPÉCT or SPÉCT/CT.	
SPC section 4.2 Line168	1	Comment: Presentation modified to be consistent with line 154 : Proposed change (if any): ~~If the~~ For the dual phase technique ~~is used~~, 370 to 740 MBq of technetium (^{99m}Tc).....	Acceptable.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
SPC section 4.3 Line178	1	Comment: should be added the contra indications mentioned in section 4.4. Proposed change (if any): In myocardial scintigraphy investigations under stress conditions, the general contraindications associated with the induction of ergometric or pharmacological stress should be considered.	Accepted.
SPC section 4.4 Lines 190, 194 and 203	1	Comment: Populations and Indications should be written in italics in order to clearly identify subsections especially for “Cardiac imaging” in “Patient preparation”, or /and “Patient preparation” could be in bold to highlight the fact that “Cardiac imaging” is part of this subsection. Proposed change (if any): *Paediatric population* …….. **Patient preparation** The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation. *Cardiac imaging* If possible, patients should fast for at least four hours prior to the study…..	Not accepted. Highlight or italics can be used. According to QRD conventions bold should not be used.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
SPC section 4.4 Line 208	1	Comment: the precautions regarding stress test stated in Warnings should be replaced by a more specific warning with the recommendation of the insertion of an intravenous flexible indwelling catheter in Patient preparation/ Cardiac imaging. **Patient preparation** The patient should be well …….examination in order to reduce radiation. *Cardiac imaging* If possible, patients should fast … prior to the study. It is recommended that patients eat a light fatty meal…. resulting in less liver activity in the image. When performing the cardiac stress test (exercise, pharmacological, electrical), strict cardiological monitoring and the material required for emergency treatment are essential. The insertion of an intravenous flexible indwelling catheter is recommended during the entire examination.	Not accepted. The SmPC does not provide instruction for general practice.
SmPC section 4.4 Line 212	1	Comment: the term Scintimammography does not seem correct. Proposed change (if any): Breast lesions less than 1 cm in diameter may not all be detected with ~~scinti~~mammoscintigraphy.	Not accepted. See previous comment.
SmPC section 4.4 Lines 221-224	1	Comment: to be deleted because already stated in the subsection Potential for hypersensitivity or anaphylactic reactions Proposed change (if any): Warnings~~If a hypersensitivity or an anaphylactic reaction~~	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		occurs, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.	
SmPC section 4.4 Lines 230 -234	1	Comment: The two proposals being antinomic, should be proposed as choices depending on the product. Proposed change (if any): <This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium- free'>. or <Depending on the time when you administer the injection, the content of sodium given to the patient may in some cases be greater than 1 mmol. This should be taken into account in patient on low sodium diet.>	Accepted. The second statement always follows the first statement. The statements can be optional but both statements should be together.
SmPC section 4.4 Line 252	1	Comment: see General remarks Proposed change (if any): 4.6 **~~Fertility,~~ Fecundity, pregnancy and lactation**	Not accepted. This is a standard QRD term.
SmPC section 4.4 Line 266	1	Comment: see General remarks Proposed change (if any): ~~Breastfeeding~~lactation	Not accepted. This is a standard QRD term.
SmPC section 4.6 Line 252	1	Comment: see General remarks Proposed change (if any	Not accepted. This is a standard QRD term.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		~~Fertility~~Fecundity	
SmPC section 4.8 Line 318	1	Comment : mistake in the calculation of the effective dose resulting from the administration of a maximal recommended activity of 2,000 MBq (consistency with section 11): Proposed change (if any): *Other disorder* Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is ~~16.3~~ 16.4mSv when the maximal recommended activity of 2000 MBq (500 at rest and 1500 MBq at stress) for a 1-day-protocol is administered these adverse reactions are expected to occur with a low probability.	Accepted.
SmPC section 5.2 line 345	1	Comment: in the formula the symbol + is too far from the brackets. Proposed change (if any) (^{99m}Tc) $(MIBI)_6^+$	Accepted.
SmPC section 6.6 Lines 453	1	Comment: according to the Core SPC for Radiopharmaceuticals, the order of the information should be as follows. In order to avoid redundancy, the text has been proposed slightly modified regarding the adequate shielding: Proposed change (if any): ~~The content of the kit before extemporary preparation is not~~	Partially accepted. Proposed change (if any): ~~The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc), is added, adequate shielding of the final preparation must be maintained.~~

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		~~radioactive. However, after sodium pertechnetate (^{99m}Tc), is added, adequate shielding of the final preparation must be maintained.~~ For instructions on extemporary preparation of the medicinal product before administration, see section 12. If at any time in the preparation of this product the integrity of this vial is compromised it should not be used. Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. ~~Adequate shielding is mandatory~~. The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc), is added, adequate shielding of the final preparation is mandatory and must be maintained.	For instructions on extemporary preparation of the medicinal product before administration, see section 12. If at any time in the preparation of this product the integrity of this vial is compromised it should not be used. Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory. The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc), is added, adequate shielding of the final preparation is mandatory and must be maintained.
SmPC section 6.6 Line 463	1	Comment: see general remarks Proposed change (if any): The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting ~~etc.~~ or any other biological fluids.	Accepted.
SmPC section 11 Lines 506	1	Comment: simplification of the sentence Proposed change (if any):	Accepted. The paragraph has been modified.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		For ~~an~~ this administered activity of 2,000 MBq ~~(500 MBq at rest and 1,500 MBq at exercise),~~ the typical radiation dose to the target organ heart is 14 mGy…	
SmPC section 11 Lines 513	1	Comment: simplification of the sentence Proposed change (if any): For ~~an~~ this administered activity of 1,800 MBq ~~(900 MBq at rest and 900 MBq at exercise)~~ , the typical radiation dose …..	Accepted. The paragraph has been modified.
SmPC section 11 Lines 517	1	Comment: as above Proposed change (if any): ~~*Scinti*~~*mammo*Scinti*graphy*	Not accepted. See previous comment.
SmPC section 12 Lines 535	1	Comment: according to the CoreSPC for Radiopharmaceuticals, the general warning should be stated. Proposed change (if any): Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system. If the integrity of this vial is compromised, the product should not be used. Instructions for preparation of technetium (^{99m}Tc) sestamibi *[Product specific]* *Information on the appearance of the reconstituted/prepared*	Accepted. The warning has been included.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		parenteral solution should appear here.] Quality control *[Product specific]*	
PIL Section 1	1	Comment: It could be more patient friendly to explain first the procedure and then the indication of the product. Proposed change (if any): After X is injected, it temporarily collects in certain parts of the body. This radiopharmaceutical substance contains a small amount of radioactivity, which can be detected from outside of the body by using special cameras. Your nuclear medicine doctor will then take an image (scans) ~~(scintigraphy)~~ of the concerned organ which can give your doctor valuable information about the structure and the function of this organ or the location of e.g., a tumour. X is used to study the heart function and blood flow (myocardial perfusion) ~~by making an image of the heart (scintigraphy)~~, for example in the detection of heart attacks (myocardial infarctions) or when a disease causes reduced blood supply to (a part of) the heart muscle (ischaemia). . X is also used in the diagnosis of breast abnormalities in addition to other diagnostic methods when the results are unclear. X can also be used to find the position of overactive parathyroid glands (glands that secrete the hormone that controls blood calcium levels).	Not accepted. The word “scans” can have multiple meanings. Not accepted.
PIL section 1	1	Comment: deletion of the brackets because there is no necessity of choice. Small amounts should be specified to be	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 638		consistent with the subsection above and section 3. Proposed change (if any): The use of X does involve exposure to ~~<~~small~~>~~ amounts of radioactivity. …….	
PIL section 2 Line 646	1	Comment: addition of X and sestamibi (more appropriate than Tetrakis) in order to comply with the Core PIL for Radiopharmaceuticals and to list all the substance involved in allergic reactions. Proposed change (if any): if you are allergic to X, ~~Tetrakis~~ tetrakis (1 isocyanide-2-methoxy-2-methylpropyl-) copper(I)] tetrafluoroborate, or sestamibi or any of the other ingredients of this medicine (listed in section 6).	Accepted.
PIL section 2 Line 659	1	Comment: information put in chronological order Proposed change (if any): **Before X administration you should:** ~~– drink plenty of water before the start of the examination in order to urinate as often as possible during the first hours after the study.~~ – be fasting for at least 4 hours if the product is going to be used to perform images of your heart – drink plenty of water before the start of the examination in order to urinate as often as possible during the first hours after the study.	Accepted.
PIL section 2	1	Comment: This is not a precautions to be taken by the patient	Not accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 675		after the procedure , it would be more appropriate to move it to section 5 in After the administration. Proposed change (if any): **X with food and drink** If the product is going to be used to perform images of your heart, then you will be asked not to eat anything for at least 4 hours before the test.~~After the injection, but before the image (scintigraphy) is made, you will be asked to eat a light fatty meal, if possible, or to drink one or two glasses of milk in order to decrease the radioactivity in your liver and to improve the image~~	
PIL section 2 line 699 and 700	1	Comment: in Pregnancy and breast-feeding, deletion of the sentence because already mentioned under the subtitle Proposed change (if any):~~If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before taking this medicine~~	Accepted.
PIL section 2 line 705	1	Comment: When the sodium content of the **administration** (not of the vial) is less than 23 mg, this sentence can be omitted. However sodium content depending on the vial content and on the reconstitution volume of sodium pertechnetate , the sentence where sodium is more than 23 mg is missing .	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): <The administration of this medicine can contain more than 23 mg of sodium. This should be taken into account if you are on low sodium diet. Please ask to the nuclear medicine doctor>	
PIL section 3 Line 718	1	Comment: “Becquerel”has a typographical error. Proposed change (if any): The quantity usually recommended to be administered for an adult ranges depending on the test to be performed, and ranges between 200 and 2000 MBq (~~megabecquerel~~Megabecquerel, the unit used to express radioactivity).	Accepted.
PIL section 3 line 725	1	Comment: wording put in a more patient friendly way and more appropriate for mammoscintigraphy (if the injection in the foot is still uptodate) Proposed change (if any): **Administration of** X **and conduct of the procedure** X is administered~~ by intravenous administration~~in a vein of the ~~t~~ arm or of the foot.	Acceptable but intravenous will be included in brakets.
PIL section line 754	1	Comment: moved from subsection Drink and Food and put in chronological order. Proposed change (if any): **After administration of X has been performed,~~ you should~~:**	Not accepted. The order is considered correct.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		– After the injection, but before the image (scintigraphy) is made, you will be asked to eat a light fatty meal, if possible, or to drink one or two glasses of milk in order to decrease the radioactivity in your liver and to improve the image. – ~~you should avoid any close contact with young children and pregnant women for the 24 hours following the injection~~ – You should urinate frequently in order to eliminate the product from your body. – you should avoid any close contact with young children and pregnant women for the 24 hours following the injection.	
PIL section 3 line 762	1	Comment: can be more than a single dose depending of the indication. Proposed change (if any): An overdose is almost impossible because you will only receive a ~~single~~ dose of X precisely controlled by the nuclear medicine doctor supervising the procedure.	Accepted.
PIL section 4 line table	1	Comment: replacement of Erythema multiforme by a more friendly term Proposed change (if any): ~~Erythema multiforme,~~redness	Not accepted. The correct definition is included.
PIL section 4 line 788	1	Comment: according to CorePIL for Radiopharmaceuticals, Proposed change (if any): This radiopharmaceutical will deliver low amounts of ionising radiation associated with with the least risk of cancer	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
PIL section 5 line 800	1	Comment: Adition of < > because this information is not necessary when the SPC is provided as User Leaflet together with the PIL in the packaging, therefore could be optional if the SPC is provided . Proposed change (if any): <The information is intended for the specialist only.> This medicine must not be used after the expiry date which is stated on the <label> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.> <This medicine will not be used if it is noticed {description of the visible signs of deterioration}.>	Not accepted. The PIL is designed for the patient. It is important for the patient to know that the information is addressed for specialists. Thus, the sentence is not optional.
Line 9	2	Comment: State quantity of stannous chloride Proposed change (if any): … tetrafluoroborate and […] mg stannous chloride [dihydrate]…	Not accepted. We strongly disagree with Dr James Ballingers proposal that the quantity of the reducing agent (usually stannous chloride) should be detailed in the SmPC of the Radiopharmaceuticals. First exact product composition may be an industrial secret. And, product stability and sensitivity to the quality of the pertechnetate used in reconstitution all is scrutinized by the quality departments prior to granting a MA. Finally, it would have no consequences as the composition should not be altered by the end user.
Line 166	2	Comment: The maximum activity of 740 MBq is not consistent with the maximum of 700 MBq stated in line 79 and used in	Accepted. Statement has been amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		estimation of dosimetry in line 525 Proposed change (if any): 500 to 700 MBq	
Section 4.2 (lines 128 – 133)	3	Comment: Image acquisition, subsection "Cardiac Imaging": waiting time of "60 min", this value should be replaced by **"30 – 60 min"**. Proposed change (if any): We propose the following wording: *"Imaging should (may) begin 30-60 min after injection to allow for hepatobiliary clearance; longer delays can be required for resting images and for stress with vasodilators alone because of the risk of higher subdiaphragmatic technetium (^{99m}Tc) activity…."* (References to EANM/ESC guidelines can support this statement).	Accepted.
Section 4.2 (lines 105 – 110)	3	Comment: In section 4.2 now the new paediatric EANM dosage card is implemented; however, the parathyroid imaging scintigraphy is not covered in this table. Should we nevertheless implement this table? Proposed change (if any):	As stated in the introduction, the activities to be administered to children and to adolescents may be calculated according to the EANM Dosage Card [Lassmann M et al. Eur J Nucl Med Mol Imaging (2008) 35:1667]. As there would be seven different tables to be included and the number of pediatric patients would be less than 1 percent of the patients treated with technetium (99mTc) sestamibi and the dosage card will be revisited in the near future, the tables will not be included in this core SmPC.
Section 4.4 SmPC (lines 216 – 218) as well mentioned	3	Comment: In section 4.4 the following sentence is now inserted (as now required in the EMA core guideline for radiopharmaceuticals): *"Close contact with infants and pregnant women should be restricted during the initial **24***	The suggested time of 24 hours covers most if not all possible scintigraphy imaging methods.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
in the PIL; lines 754)		***hours***. “ What is the justification of this calculated value? Proposed change (if any):	