25 June 2015
EMA/219347/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on core SmPC and package leaflet for sodium fluoride (18F)' (EMA/CHMP/465616/2014)

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

Stakeholder no.	Name of organisation or individual
1	AIPES (Association of Imaging Producers and Equipment Suppliers) – European Industrial Association for Nuclear Medicine and Molecular Healthcare. • *AAA • **CIS BIO INTERNATIONAL
2	Florence Rigal (Individual)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Line 141** Comment : According to the Guideline on CoreSPC (2009), "In case of restricted medical prescription, this section should be started by specifying the conditions. In case of specific safety need, any recommended restriction to a particular setting should also be stated (e.g. "*restricted to hospital use only*" ….."). Please refer also to EMA QRD Template for CP, Annex II stating **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE** <Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).> <Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).> Therefore whatever the radiophamaceutical used, it should be specified at least in any CoreSPC for RP: Proposed change (if any): This medicinal product is intended for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel. <This procedure should be requested by <physicians , specialists> skilled in the clinical management of < product specific>>	Not accepted. This section already has standard QRD sentences which already cover all types of medicinal products. Therefore, there is no need for further recommendations. The second proposed sentence in brackets was not considered appropriate.
1	line 161** The origin and date of the data should be specified in order to check easily if the document is still up-to-date. Proposed change (if any):	Accepted. The sentence has been modified to include the following: {include date of dosage card}

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The activities to be administered to children and adolescents may be calculated according to the recommendations of the EANM paediatric task group (Dosage Card 2014); the activity administered …….	
1	Line 382** Comment : **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…. Proposed : The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, ~~etc~~ other biological fluids. Radiation protection precautions in accordance with national regulations must therefore be taken.	Accepted.
1	Line 429*,** Comment: **In all templates concerning radiopharmaceuticals, in section** 12 The sentence is not correct because the vial (singular) should never be opened even after disinfecting. Proposed change (if any): The vial must not be opened . After ~~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.	Accepted.
1	PIL section 5** Concerns all products for hospital use . This information should be optional because not necessary for the	Accepted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	product whose packaging includes the SPC also. Proposed change (if any): **<u>≤</u>**The following information is intended for the specialist only. 653 This medicine must not be used after the expiry date which is stated on the label.**>**	
2	The proposed package leaflet is not aligned with the Core Package leaflet for radiopharmaceuticals: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/10/WC500115503.pdf While EMA has rightfully recognised that specific wording should be used for drug products used by healthcare professionals (instead of directly by the patient) for radiopharmaceuticals. This wording was not used for NaF. This wording should also be added as an alternative in the QRD. It existence is kept quite confidential since it is listed as being only for radiopharmaceuticals, while it should much wider spread to include all products administered by healthcare professionals.	Accepted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 107 + 109**	1	Comment: section 2 Redundancy to be deleted Units depending on the radioactive concentration of the product Proposed change (if any): One ~~Each~~ mL contains xxxx [GBq/MBq] of sodium fluoride (^{18}F) at date and time of calibration. The activity per vial ranges from <XXX> [GBq/MBq]to <XXX> [GBq/MBq] at the date and time of calibration	• *AAA • **CIS BIO INTERNATIONAL Accepted.
Line 115 * **	1	Comment Information product specific. Ions to be deleted Proposed change (if any): Excipient(s) with known effect: Each mL contains ~~3.57~~ XXX mg of sodium ~~ions~~.	Agreed to delete the quantity as this is product specific. However, the word “ions” is kept as it designates that it is not in metal form.
Lines 145-147*,**	1	Comment:section 4.2 Proposal to improve clarity. : ”image” should be replaced by activity. CT should be written in clear for the first use The route of administration should be moved to Method of administration Proposed change (if any): The mean recommended activity for an adult	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		weighing 70 kg is 370 MBq ~~(the activity will be adapted to~~ but can vary from 100-400 MBq depending on the bodymass, the type of camera used, PET/CT (computed tomography), and acquisition mode~~. The image could vary from 100-400 MBq), administered by direct intravenous injection.~~	
Line 164**	1	Comment: The written data is from EANM dosage card 2008. According to EANM dosage card **2014** and Lassmann EJNM February 2014 there is **Only one baseline value (for 3D)** "The baseline value for the calculation of the activities to administer is set to 10.5 MBq. The EANM dosage card entry "F-18 Fluorine (2D)" will be deleted. » Proposed change (if any): A[MBq]Administered = ~~Baseline Activity~~ 10.5 X Coefficient	Not accepted. The general sentence is for 2D as well, although we acknowledge most will use the value for 3D. We prefer to keep the sentence as general recommendation.
Line 166 -167**	1	Comment Reformulation for better clarity but please note that according to EANM 2014, only values for PET 3D are provided. Proposed change (if any): **A minimum activity of 14 MBq is recommended in case of acquisition with 3D PET system** and 26 MBq in the case of acquisition with 2D PET system. In children	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		images acquisition in 3D mode should be preferred.	
Line 172-181 **	1	Comment: According to the Guidelines on SPC for Radiopharmaceuticals (2011), addition of the route of administration and kind of use directions for proper use by healthcare professionals should be stated after *<Precautions to be taken before handling or administering the medicinal product>* Proposed change (if any): Method of administration For intravenous use For < multidose / single use> *Precautions to be taken before handling or administration of the medicinal product* For instructions on dilution of the medicinal product before administration, see section 12. For patient preparation, see section 4.4. The activity of sodium fluoride (^{18}F) has to be measured with an activimeter immediately prior to injection. The injection of sodium fluoride (^{18}F) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts .	Not accepted. The statement should be in accordance with the QRD template. This information will be included in section 6.5, thus the information will be repetitive.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 184**	1	Proposed change (if any): Image acquisition The emission scans are usually started 60 minutes after the injection of sodium fluoride (^{18}F). Provided a sufficient activity remains for adequate counting statistics, ~~sodium fluoride (^{18}F) PET~~ scans can also be performed up to two or three hours after administration, thus reducing background activity. Voiding immediately prior to imaging is recommended in order to reduce the activity in the pelvis.	Not accepted. The word “scan” is more generic and can be used for any other type of procedure eg contract media, etc..). It is important to be specific here with the term used. Thus, we propose to keep it as is.
Line 205**	1	Comment: In the case of sodium fluoride (18F), no paediatric data is provided in section 5.1. Proposed change (if any): Paediatric population For information on the use in paediatric population, see section 4.2 ~~and 5.1~~.	Agreed.
Lines 210-211**	1	Comment: It is important that the patient urinate just before the scans for the acquisition of images of good quality . Proposed change (if any): Patient preparation The patient should be well hydrated before the start of the examination and urged to void just before the	Agreed with some changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		scans and as often as possible during the first hours after the study in order to obtain images of good quality and to reduce radiation exposure.	
Line 231*	1	Comment : koma to be deleted. Proposed. Depending on the time when you administer the injection,	Agreed.
Line 252**	1	Pregnancy The use of sodium fluoride (^{18}F) is contraindicated in pregnant women due to the radiation exposure to the foetus (see section 4.3.)	Agreed.
Line 263**	1	According to the EMA QRD template : Proposed : Fertility No studies on fertility have been performed.	Agreed.
Line 272 *,**	1	Comment: 4.8: the maximal posology stated in section 4.2 is 400 MBq. The effective dose should be recalculated according to the dosimetry data published in the addendum N° 4 de l'ICRP 53: 0.017x 400 = 6.8 mSv	Accepted, but we will require decimal values.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): As the effective dose is ~~8.9~~ 6.8 mSv when the maximal recommended activity of ~~350~~400 MBq is administered for an adult of 70 kg, these adverse reactions are expected to occur with a low probability.	
Line 296**	1	Comment: According to the EMA QRD template, the Mechanism of action should be stated here. Thus the text lines 311 to 316 should be moved here. Proposed: **5.1. Pharmacodynamic properties** Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX06 Mechanism of action Due to its affinity to bone mineral sodium fluoride (^{18}F) becomes 3 – 10 times more incorporated into bone regions affected by malignant processes with resulting osteoblastic activity or osteolytic defects than in non-affected recumbent bone. Non-cancerous traumatic, erosive or inflammatory lesions of bone structure are also connected with increased osteogenesis. Sodium fluoride (^{18}F) therefore is a marker of bone reactive processes of cancerous or traumatic affliction. It detects non-malignant regions of	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		physiologically or pathologically enhanced bone metabolism as well.	
Lines 311-316**	1	Organ uptake: deletion of sentences moved in Mechanism of action	Agreed.
Line 347**	1	Comment:6.2 Incompatibilities Product specific. These sentences should be optional depending on the possibility of dilution. Dilution is depending on the radioactive concentration of the product. Dilution can be not indicated. Proposed change (if any): <In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.> <This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.>	Agreed.
Line 367**	1	Comment: According to EMA QRD Template , the packsize should be specified Proposed change (if any): Pack size: One <multidose> vial contains <**X>** to <**XXX>** mL of solution, corresponding to <**XXX>** to <**XXX>** GBq/MBq at calibration time.	Agreed with some modifications.
Line 380 *,**	1	Comment:section 6.6 According to the Guideline on CorSPC for Radiopharmaceuticals	Agreed with slight change.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): If the integrity of the 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.	
Line 382**	1	Comment: 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…. Proposed change (if any): The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, or any other biological fluids. Radiation protection precautions in accordance with national regulations must therefore be taken.	Agreed.
Lines 407_419*, **	1	Comment: - More recent data are provided in ICRP 53, 4th addendum of 24th May 2013 53 (ICRP Ref 4832-4937-0900 May 24 2013, Revised Feb 24 2014). => different absorbed doses and different effective doses - Assumptions have been added.	Not agreed to add new paragraph. But it is agreed to specify that the data is from the “4th addendum” and to add the new table with usual decimal notation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome

- The maximal recommended activity for 2D is 400 MBq instead of 370 MBq.

Proposed change (if any):

Data listed below are from ICRP 53 fourth addendum Publication ~~and ICRP 80 Publication~~ and are calculated according to the following assumptions: .

^{18}F-fluoride is a highly effective bone-seeking PET tracer used for detection of skeletal abnormalities. The uptake mechanism of 18F-fluoride resembles that of ^{99m}Tc-methylene diphosphonate (MDP), but has better pharmacokinetic characteristics, including faster blood clearance and 2-fold higher uptake in bone. Uptake of ^{18}F-fluoride reflects blood flow and bone remodeling.

Absorbed dose per unit activity administered (mGy/MBq)

Adult	15 year	10 year	5 year	1 year
6.7E-03	8.8E-03	1.3E-02	2.0E-02	3.9E-02
1.5E-01	1.9E-01	2.8E-01	3.9E-01	5.4E-01
9.4E-02	7.5E-02	1.2E-01	2.1E-01	4.8E-01
6.6E-03	7.5E-03	1.1E-02	1.6E-02	2.5E-02
2.9E-03	3.7E-03	6.0E-03	9.5E-03	1.8E-02
4.2E-03	5.1E-03	8.2E-03	1.2E-02	2.3E-02
3.7E-03	4.6E-03	7.9E-03	1.1E-02	2.0E-02
5.8E-03	7.5E-03	1.1E-02	1.7E-02	3.0E-02
6.8E-03	8.4E-03	1.3E-02	1.9E-02	3.0E-02

Line no.	Stakeholder no.	Comment and rationale; proposed changes					Outcome
		(Upper large	5.1E-03	6.3E-03	1.0E-02	1.5E-02	2.6E-02)
		(Lower large	9.1E-03	1.1E-02	1.7E-02	2.5E-02	3.7E-02)
		Heart	4.2E-03	5.1E-03	7.9E-03	1.2E-02	2.2E-02
		Kidneys	1.3E-02	1.6E-02	2.4E-02	3.6E-02	6.7E-02
		Liver	4.0E-03	5.2E-03	7.8E-03	1.2E-02	2.3E-02
		Lungs	4.5E-03	5.8E-03	8.6E-03	1.3E-02	2.6E-02
		Muscles	5.8E-03	7.1E-03	1.1E-02	1.6E-02	2.8E-02
		Oesophagus	3.7E-03	4.8E-03	7.2E-03	1.1E-02	2.2E-02
		Ovaries	8.3E-03	1.1E-02	1.5E-02	2.2E-02	3.6E-02
		Pancreas	5.0E-03	6.1E-03	9.2E-03	1.4E-02	2.7E-02
		Red marrow	3.7E-02	3.9E-02	7.6E-02	1.8E-01	4.4E-01
		Skin	4.1E-03	4.9E-03	7.7E-03	1.2E-02	2.2E-02
		Spleen	4.2E-03	5.5E-03	8.4E-03	1.3E-02	2.6E-02
		Testes	6.1E-03	8.3E-03	1.4E-02	2.0E-02	3.2E-02
		Thymus	3.7E-03	4.8E-03	7.2E-03	1.1E-02	2.2E-02
		Thyroid	4.9E-03	5.7E-03	8.1E-03	1.2E-02	2.0E-02
		Uterus	1.3E-02	1.5E-02	2.4E-02	3.5E-02	5.0E-02
		Remaining	5.9E-03	7.3E-03	1.1E-02	1.7E-02	2.8E-02
		EEffective dose (mSv/MBq)	**1.7E-02**	**2.0E-03**	**3.3E-02**	**5.6E-02**	**1.1E-01**
		If PET with sodium fluoride (^{18}F) is acquired in 2D mode, the effective dose resulting from the administration of a recommended activity of ~~370~~400 MBq for an adult weighing 70 kg is about ~~8.9~~6.8mSv. For an administered activity of ~~370~~400 MBq, the typical radiation dose/doses to the critical organ/organs (bladder, bone surfaces, red marrow, kidneys and uterus) are~~81~~60, ~~15~~38, 15, ~~7.4~~5 and ~~7~~ 5						

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		mGy If PET with sodium fluoride (^{18}F) is acquired in 3D mode, the effective dose resulting from the 417 administration of a recommended activity of 200 MBq for an adult weighing 70 kg is about ~~4.8~~ 3.4 mSv. 418 For an administered activity of 200 MBq the typical radiation dose/doses to the critical organ/organs 419 (bladder, bone surfaces, red marrow, kidneys and uterus) are~~44~~30, ~~8~~19, 8, ~~4~~ 3 and ~~3.8~~3 mGy, respectively.	
Line 427**	1	Comment: the possibility of dilution is optional because is product specific, depending on the radioactive concentration Proposed change (if any): <The medicinal product may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection.>	Partially agree. The recommendation is according to the Pharmacopeia
Line 429*,**	1	Comment: The sentence is not correct because the vial (singular) should never be opened even after disinfecting. Proposed change (if any): The vial must not be opened . After ~~before~~ disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding	Agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and a disposable sterile needleor using an authorised automated application system.	
Line 433*	1	Comment: Proposed change (if any): ~~As with any pharmaceutical product,~~ If the integrity of this vial is compromised, the product should not be used.	Agreed.
Line 440**	1	Comment:Product not registered in Centralised Procedure Proposed change (if any): Detailed information on this medicinal product is available on the website of the ~~European Medicines Agency~~ http://www.ema.europa.eu ~~}~~ {name of MS/Agency}>	Not agreed but have modified the sentence by adding the proposed change as optional.
PIL *,**	1	Comment: EMA QRD Template 2013 and Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011) Proposed change (if any): ~~{Active substance(s)}~~ sodium fluoride (^{18}F) **Read all of this leaflet carefully before you will be administered this medicine. because it contains important information for you.**- Keep this leaflet. You may need to read it again. - If you have any further questions, ask your	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		referring doctor or the ~~specialist physician in~~ nuclear medicine doctor who will supervise the procedure. If you get any ~~of the~~ side effects, talk to your nuclear medicine doctor. This includes any possibleside effects not listed in this leaflet. Voir rubrique 4. **What is in this leaflet**: 1. What X is and what it is used for 2. ~~Before X is administered~~What you need to know before X is used	
Line 521 -522**	1	Comment: EMA Annotated QRD Template 2013 and use of friendly term Proposed change (if any): X contains the active substance sodium fluoride (^{18}F). This medicine is a radiopharmaceutical product (radioactive medicine) for diagnostic use only.	Agreed.
Line 534**	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011) Proposed change (if any): The use of X does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the benefit of this procedure with the radiopharmaceutical outweighs the risk of being exposed to radiation.	Agreed.
Line 535*	1	Comment: Guideline on CoreSmPC and PIL for	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Radiopharmaceuticals (2011) Proposed change (if any): 2.<u>What you need to know before X is used</u>	
Line 537**		Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011) Proposed change (if any): **<u>X must not be used</u>** instead of « Do not take X »	
Line 5	1	Comment: : Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Product not intended to be labelled. Proposed change (if any): if you are allergic (hypersensitive) to sodium fluoride (^{18}F) or any of the other ingredients of X ~~or to any of the components of the labelled radiopharmaceutical~~ <u>listed in section 6</u>	Agreed.
Line 541	1	Comment: consistency with SPC section 4.6 Proposed change (if any): if you are pregnant <u>or think you may be pregnant. Inform your nuclear medicine doctor if you are concerned.</u>	Agreed with changes
Line 547-550**	1	Comment: Pregnancy is an absolute contraindication which should be mentioned in “X must not be used”	Agreed with changes

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Warning for renal failure should be added. Proposed change (if any): Inform your nuclear medicine doctor before you are given X in the following cases; - ~~if you are pregnant or believe you may be pregnant~~ - if you are breast-feeding - if you have kidney problems	
Line 554-556*,**	1	Comment: The first sentence has corrected The warning on close contact should be moved into "After administration" Proposed change (if any): **Before X administration you should,** drink plenty of water to be well hydrated before the start of the examination in order to urinate as often as possible during the first hours after the study ~~If you come into contact with infants: It is recommended that close contact be avoided between the patient and infants in the initial 12 hours following the injection..~~	Agreed.
Line 558*	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **Children and adolescents :**	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		talk to your nuclear medicine doctor if you are under 18 years old.	
Line 559**	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **Other medicines and X** P~~lease t~~Tell ~~to~~ your nuclear medicine doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription since they may interfere with the interpretation of the images.	Agreed.
Line 567-570*,**	1	Comment: Pregnancy being an absolute contraindication, addition of a warning. Use of nuclear medicine doctor For consistency in the whole leaflet Proposed change (if any): **Pregnancy and breast-feeding** 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. **If you are pregnant** **You must not take X if you are pregnant.** It must be established that you are not pregnant before the use of this product. You must inform the ~~specialist physician in Nuclear Medicine~~ nuclear medicine doctor before the administration of X if there is a	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		possibility you might be pregnant, if you have missed your period ~~or if you are breast-feeding.~~ When in doubt, it is important to consult your ~~physician or the specialist physician in~~ nuclear medicine doctor who will supervise the procedure.	
Line 572**	1	Comment: recommendations to replace “should “ by”must” in order to avoid misunderstanding in the translation in some roman countries. Proposed change (if any): **If you are breast-feeding**, breast milk may be drawn off before injection and stored for subsequent use. 574 Breast-feeding ~~should~~ must be stopped for at least 12 hours. Any milk produced during this period should be discarded.	Not agreed.
Line 578**	1	Comment: addition of a warning on close contact in consistency with the CoreSPC section 4.6 Proposed change (if any): It is recommended that you avoid close contact with infants in the initial 12 hours following the injection.	Agreed.
Line 585**	1	Comment: Proposed change (if any): This medicine contains sodium (x mg/mL). If the	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		content of sodium is greater than 1 mmol (up to 23 mg per dose), this should be taken into account if you are with a low sodium diet	
Line 587*	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **3. How ~~to <take> <use>~~ X is used**	Agreed.
Line 595-597*,**	1	Comment: - Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). - The recommended posology is 370 MBq. Proposed change (if any): The nuclear medicine doctor supervising the procedure will decide on the quantity of X to be used in your 595 case. It will be the ~~minimal~~ smallest quantity necessary to get the desired information. ~~596 The quantity to be administered usually recommended for an adult ranges from 2 to 5 MBq/kg of body~~ ~~597 mass.~~The usual amount recommended for an adult is 370 MBq. Megabecquerel (MBq) is the unit used to express radioactivity	Agreed with changes.
Line 600**	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **Use in children**	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		600 In ~~case of paediatric population~~ children and adolescents,, the quantity to be administered will be adapted to the child's body mass.	
Line 603*	1	**Administration of X and conduct of the procedure** 603 X~~ is administered by single intravenous injection~~ is given as an injection into your vein (intravenous injection). One injection is sufficient to carry out the scan that your doctor needs.	Not agreed. It is felt that the wording clear enough and no change is required.
Line 606-607**	1	Comment: - In consistency with SPC section 4.2 - Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **Duration of the procedure** Your nuclear medicine doctor ~~supervising the procedure~~ will inform you about the usual duration of the procedure A scan is usually taken about 60 minutes and up to 3 hours after the injection, depending on the procedure. After injection, you will be offered a drink and asked to urinate immediately preceding the test.	Agreed with changes.
Line 610*,**	1	Comment: In consistency with SPC section 4.4 The term should has to be replaced by must in order to avoid the use of conditional in roman languages translation Proposed change (if any):	Must is not agreed. The rest is agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		After administration of X , you~~should~~ must: • avoid any close contact with young children and pregnant women for the 12 hours following the injection	
Line 616 – 623*,**	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **If you have been ~~administered~~given more X than you should** An overdose is almost impossible because you will only receive a single dose of X precisely controlled by the ~~specialist physician~~nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. The elimination of the radioactive constituents should be increased as much as possible. You should drink as much as possible and frequently empty your bladder. It may become necessary to take diuretics. ~~622 Should you have any further question on the use of X, please ask if the nuclear medicine doctor who~~ 623 ~~supervises the procedure~~. If you have any further question on the use of X, please ask your nuclear medicine doctor who supervises the procedure.	"Given" not accepted. Agreed with changes.
Line 627 – 629**	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any):	Not agreed as only when the product is administered that the ionising radiation will be delivered.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		4. Possible side effects Like all medicines, ~~X~~this medicine can cause side effects, although not everybody gets them. No serious adverse effects have been observed to date. ~~This administered~~ The radiopharmaceutical will deliver low amounts of ionising radiation with very low risk of cancer and hereditary abnormalities.	
Line 632*	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). : information moved in section 1 Proposed change (if any): ~~Your doctor has considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical overcomes the risk due to radiation.~~	Agreed.
Line 635*,**	1	Comment: EMA QRD Template: moved to line 640. Proposed change (if any): ~~If you get any side effect, please tell your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet.~~	Agreed.
Line 647*	1	Comment: Guideline on CoreSmPC and PIL for Radiopharmaceuticals (2011). Proposed change (if any): **How ~~to store~~ X is stored**	Agreed.
Line 652*,**	1	Comment: Guideline on CoreSmPC and PIL for	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Radiopharmaceuticals (2011). This information should be optional because not necessary for the product whose packaging includes the SPC also. Proposed change (if any): <u><</u>The <u>following</u> information is intended for the specialist only. 653 ~~Do not use this medicine after the expiry date which is stated on the label after {DD MM YYYY~~<u>This medicine must not be used after the expiry date which is stated on the label</u>.>	
Line 660 – 666*,**	1	Comment: This information is product specific. Proposed change (if any): **What X contains** - The active substance is sodium fluoride (^{18}F). One mL contains ~~2.0~~ <u>X</u> GBq<u>/MBq</u> of sodium fluoride (^{18}F) at date and time of production - The other ingredients are ~~water for injection, sodium chloride and potassium dihydrogen phosphate.~~ **What X looks like and contents of the pack** The total activity of the vial at that time is therefore between ~~0.37~~ GBq<u>/MBq</u> and ~~22.0~~ GBq<u>/MBq</u>.	Agreed Agreed.
Line 682 – 692 **	1	Comment: not appropriate for drugs containing this active substance.	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): <~~This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.~~ ~~The European Medicines Agency will review new information on the medicine every year and this leaflet will be updated as necessary.>~~ ~~This medicine has been authorised under 'exceptional Circumstances'. This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine.~~ ~~The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.>~~	
Line 696 – 699**	1	Comment: the EMA QRD Template for Centralised Procedure is not appropriate for the sodium fluoride. Please refer to the template for referral procedures Proposed change (if any): **<Other sources of information>** ~~Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu <There are also~~	Not agreed but made some minor change where the sentence is optional.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~links to other websites about rare diseases and treatments.>~~ ~~<This leaflet is available in all EU/EEA languages on the European Medicines Agency website.>~~Detailed information on this medicine is available on the website of {name of MS/Agency}>	
Line 703**	1	Comment: EMA QRD Template Proposed change (if any): <The following information is intended for ~~medical or~~ healthcare professionals only:>	No accepted as this is part of the template.