22 September 2017
EMA/630247/2017
Committee for Medicinal Products for Human Use (CHMP)

Submission of comments on 'Guideline on core SmPC and Package Leaflet for sodium iodide (^{131}I) therapy capsule' (EMA/CHMP/649301/2016)

Comments from:

Name of organisation or individual
CIS bio international BP 32 91192 Gif sur Yvette Cedex France

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	SPC /PIL Typing error in the whole text : sodium iodide (^{131}I) instead of (131I)	corrected

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
SmPC section 2 Line 77		Comment: wording used by Guideline on CoreSPC for Radiopharmaceuticals, "*Please insert the strength at the **date** and time **of calibration**"* Proposed change (if any): One capsule contains sodium iodide (^{131}I) [...] – [...] MBq at ~~activity reference time~~calibration date.	Accepted, added: *at time of calibration*
SmPC section 4.2 Line 112		Comment: According to the Royal College of Physicians page 8, radioiodine treatment of hyperthyroidism is expected to restore euthyroidism in 50-75% of patients within 6 to 8 weeks of radioiodine administration i. According to EANM guideline 2010 ii section XI:"Regular review of thyroid function tests in patients who have undergone radioiodine treatment for thyroid disease is essential to assess the efficacy of the treatment and for timely detection of developing hypothyroidism or post-treatment immunogenic hyperthyroidism. First, TSH and free T4 examination should be performed not longer than 4-6 weeks after radioiodine therapy. Shorter intervals of about 2-3 weeks are recommended for patients who have received ATDs or who have an increased risk of endocrine	Accepted: *weeks* included instead of *months*

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		ophthalmopathy because of hypothyroidism". Therefore it is suggested changing "months" by "weeks", in order to increase earlier the vigilance of the physician to depict a hypothyroidism. Proposed change (if any): ~~The therapeutic effect is only achieved after several months~~. The therapeutic effect is only achieved after several weeks.	
SmPC section 4.2 Line 123		Comment : Information already given line 111. Proposed change (if any): It is usually in the range of 200-800 MBq for a patient of average weight (70 kg) but repeated treatment up to a cumulative dose of 5000 MBq may be necessary. ~~The therapeutic effect is only achieved after several months..~~	Accepted, redundancy deleted
SmPC section 4.2 Line 124		Comment: The recommended time period after which the radioiodine treatment can be repeated in case of persisting hyperthyroidism is not any more mentioned. The EANM procedure guideline for therapy of benign thyroid disease (Stokkel et al. 2010[1]) recommends repeating the radioiodine treatment after 6-12 months.	Accepted, added: *Re-treatment after 6-12 months is indicated for persisting hyperthyroidism*

[1] Stokkel MPM, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. Eur J Nucl Med Mol Imaging 2010; 37: 2218-28.

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		Proposed change (if any): The following additional sentence is proposed: "Re-treatment after 6-12 months is indicated for persisting hyperthyroidism."	
SmPC section 4.2 Lines 140 and 141		Comment: "weight" has to be replaced by "volume" according to the formula used for calculation. Proposed change (if any): In the case of Graves' disease, multifocal or disseminated autonomy, the above mentioned target organ doses are related to the overall ~~weight~~ volume of the thyroid gland ~~mass~~, however in the case of unifocal autonomy, the target organ dose is only related to the ~~weight~~volume of the adenoma. For recommended doses to target organs: see section 11.	Accepted: included: *volume* instead of *weight*
SmPC section 4.2 Lines 144		Comment: Already mentioned line 125, to be deleted. Proposed change (if any): ~~Fixed dose protocols may also be used.~~	Accepted, redundancy was deleted
SmPC section 4.2 Lines 175		Comment: The procedure to use should be given in this subsection instead of section 6.6. and redundant information should be deleted.	Accepted, added in section Method of administration: *The activity of the capsule should be determined before use. And The patients stomach should be empty when taking the capsule.* and redundancy was deleted

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Method of administration The capsule is administered orally on an empty stomach. The capsules should be swallowed whole with abundant drink to ensure clear passage into the stomach and upper small intestine. In patients with suspected gastrointestinal disease, great care should be taken when administering Sodium Iodide (131I) capsules. Concomitant use of H2-antagonists or proton pump inhibitors is advised. In case of administration to children, especially to younger children, it has to be ensured that the capsule can be swallowed whole without chewing. It is recommended to give the capsule with mashed food. **Procedure for use:** The following procedure should be used when the product is being administered to the patient: - Determine the activity before use. ~~The patients stomach should be empty when taking the capsule.~~ - The patient will receive a heavy lead pot, attached in it one capsule in a plastic single dose container ~~- The patient will unscrew the lid of the lead pot and the container cap simultaneously by turning itthree times~~	

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		~~counter-clockwise~~ - ~~The patient will remove the lid, lift the lead pot, and swallow the capsule~~[Product specific].	
SmPC section 4.4 Lines 213		Comment: according to Guideline on CoreSPC for Radiopharmaceuticals Paediatric populations should be moved from line 237 to line 213 before Patient preparation. Proposed change (if any):	Accepted/amended
SmPC section 4.4 Line 223		Comment: No recommendation is given in case of patients suffering of constipation. The EANM guideline for radioiodine therapy of differentiated thyroid cancer (Luster et al. 2008[2]) recommends using adjuvant medication with mild laxative to increase the colonic emptying rate, decreasing radiation exposure of the intestines and facilitating scan interpretation. Proposed change (if any): The following additional sentence is proposed: "To reduce colon exposure, mild laxatives (but not stool softeners which do not stimulate the bowel) may be necessary in patients having less than one bowel movement	Accepted, sentence included under Patient preparation: *To reduce colon radiation exposure, mild laxatives (but not stool softeners which do not stimulate the bowel) may be necessary in patients having less than one bowel movement a day.*

[2] Luster M, Clarke S.E, Dietlein M, Lassman M, Lind P, Oyen W, Tennvall J, Bombardieri. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2008; 35(10): 1941-59.

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		a day.”	
SmPC section 4.4 Line 237		According to Guideline on SPC for Radiopharmaceuticals (2011), information on Paediatric population should be mentioned before Patient preparation. The whole subsection regarding Paediatric population should be moved above to line 213.	Accepted/amended
SmPC section 4.4 Line 251		Comment: Replacement of “dose “by “capsule”, as written for the warning on sucrose. The alternative when sodium content is lesser than 23 mg should be proposed. Proposed change (if any): <This medicinal product contains [...] mg of sodium per ~~dose~~ **capsule**. To be taken into account by patients on a controlled sodium diet.> **<This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, i.e. essentially ‘sodium-free’.>**	Accepted/amended
SmPC section4.6 Line276		Comment: -Information about differentiated thyroid carcinoma during pregnancy should be moved into subsection Pregnancy and deleted from subsection Women of child bearing potential.	Accepted/amended

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		- Recommendations to women not to become pregnant within 6-12 months after administration should be moved from subsection Pregnancy to subsection Women of child bearing potential. Proposed change (if any): Women of child bearing potential. ……..alternative techniques not using ionising radiation (if there are any) should be offered to the patient~~. If a differentiated thyroid carcinoma is diagnosed during pregnancy, the treatment with iodine-131 should be postponed after childbirth.~~ **Women receiving Sodium Iodide (131I) should be advised not to become pregnant within 6-12 months after administration.**	
SmPC section4.6 Line292		Comment: Information about differentiated thyroid carcinoma during pregnancy is proposed to be replaced by the sentence previously mentioned in subsection Women of child bearing potential. Recommendations to women not to become pregnant within 6-12 months after administration should be moved to subsection Women of child bearing potential and deleted in Pregnancy.	Accepted/amended

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		Proposed change (if any): Pregnancy ……~~Should differentiated thyroid carcinoma be diagnosed during pregnancy, iodine-131 treatment must be 292 postponed until after the pregnancy.~~ **If a differentiated thyroid carcinoma is diagnosed during pregnancy, the treatment with iodine-131 should be postponed after childbirth.** ~~Women receiving Sodium Iodide (131I) should be advised not to become pregnant within 6-12 months after administration.~~	
SmPC section 4.6 Line 283		Comment: Age discrimination should be avoided: "young" to be deleted. Proposed change (if any): <u>Contraception in males and females</u> …….Sperm banking should be considered for ~~**young**~~ men who have extensive disease and therefore may need high iodine-131 therapeutic doses.	Accepted/amended

<table>
<tr><th>Line number(s) of the relevant text
(e.g. Lines 20-23)</th><th>Stakeholder number
(To be completed by the Agency)</th><th>Comment and rationale; proposed changes
(If changes to the wording are suggested, they should be highlighted using 'track changes')</th><th>Outcome
(To be completed by the Agency)</th></tr>
<tr><td>SmPC section4.8
Line 334</td><td></td><td>Comment: It is proposed to include “Congenital hypothyroidism” in the SOC Congenital, familial and genetic disorders in the table “Adverse reactions after treatment of benign disease”. For ref we propose “Congenital hypothyroidism due to maternal radioactive Iodine exposure during pregnancy” Kurtoglu et al. J Clin Res Pediatr Endocrinol. 2012;4(2):111-113

Proposed change (if any):

Adverse reactions after treatment of benign disease
<table>
<tr><th>System organ</th><th>Adverse reaction</th><th>Frequency</th></tr>
<tr><td>Immune system disorders</td><td>Anaphylactoid reaction</td><td>Not known</td></tr>
<tr><td rowspan="3">Endocrine disorders</td><td>Permanent hypothyroidism, hypothyroidism</td><td>Very common</td></tr>
<tr><td>Transient</td><td>Common</td></tr>
<tr><td>Thyreotoxic crisis, thyroiditis, hypoparathyroidism (blood calcium decreased, tetany)</td><td>Not known</td></tr>
</table></td><td>Accepted/amended</td></tr>
</table>

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Eye disorders	Endocrine ophthalmopathy (in Graves' disease)	Very common
	Sicca syndrome	Not known
Respiratory, thoracic and	Vocal cord paralysis	Very rare
Gastrointestinal	Sialoadenitis	Common
Congenital, familial and genetic disorders	Congenital hypothyroidism	Not known
General disorders and	Local swelling	Not known

SmPC section 4.8 Lines 344 and 345		Comment: Doses have to be updated according to ICRP 128. Update according to ICRP128 and according to Guideline on CoreSPC for Radiopharmaceuticals:<The effective dose is […] mSv when the maximal recommended activity of […] MBq is administered.> Proposed change (if any): ~~The effective dose after therapeutic doses of sodium iodide (131I) is higher than 20 mSv and the effective dose equivalent when the administered dose is 11100 MBq (with~~	Accepted/amended

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		~~thyroid 0%) is 799,2 mSv.~~ **The effective dose is 3,108 mSv when the maximal recommended activity of 11 100 MBq is administered (with thyroid uptake 0%).**	
Section 5.2 Line 460		Comment: according to Guideline on CoreSPC for Radiopharmaceuticals Proposed change (if any): ~~Organ~~ distribution and Organ –uptake	Accepted/amended
Section 6.4 Line 526		Comment: according to Guideline on CoreSPC for Radiopharmaceuticals Proposed change (if any): Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.	Accepted/amended
Section 6.6 Line 534		Comment: according to Guideline on CoreSPC for Radiopharmaceuticals Proposed change (if any): **General warning** Radiopharmaceuticals should be received,……. … If at any time in the preparation of this product the integrity of this [container] is compromised it should not be used. **Administration procedures should be carried out in a**	Accepted/amended

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		way to minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.	
Section 6.6 Line 542		Comment: according to Guideline on CoreSPC for Radiopharmaceuticals Proposed change (if any): ~~*External radiation exposure*~~ *Precautions to be taken before handling or administration of the medicinal product* The administration of sodium iodide (131I) for therapy may result in significant environmental hazard and creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered. Radiation protection precautions in accordance with national regulations should therefore be taken. ~~Administration procedures should be carried out in a way to minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.~~ This preparation is likely to result in a relatively high radiation dose to most patients. The administration of high activity may result in significant environmental hazard.	Accepted/amended in modified form to avoid redundancies

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		This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered. Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated by the patients in order to avoid any contaminations. *External radiation exposure* When opening the container …….	
Section 6.6 Line 560		Comment: Procedure for use is [Product specific] and it should be should be described in section 4.2 Method of administration. Proposed change (if any): ~~**Procedure for use:**~~ ~~The following procedure should be used when the product is being administered to the patient:~~ ~~- The patients stomach should be empty when taking the capsule.~~ ~~- The patient will receive a heavy lead pot, attached in it one capsule in a plastic single dose container~~ ~~- The patient will unscrew the lid of the lead pot and the container cap simultaneously by turning it three times counter clockwise~~ ~~- The patient will remove the lid, lift the lead pot, and~~	Accepted

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		~~swallow the capsule~~	
Section 6.6 Lines 570 to 580		Comment: Product specific information should be deleted. Proposed change (if any): **Precautions and activity data** 1.3% of iodine-131 decays via xenon-131m (half-life 12 days) and a small amount of xenon-131m activity may be present in the packaging as a result of diffusion. It is therefore recommended that the transport container be opened in a ventilated enclosure and that, after removal of the capsule, the packaging materials are allowed to stand overnight before disposal to permit the release of absorbed xenon-131m. In addition, there can be limited leakage of volatile iodine-131 activity from the capsule. ~~The container incorporates a small disc of charcoal in the lid which serves to absorb the iodine that escapes from the capsule. The charcoal disc may become contaminated with up to 1.3MBq (35gCi) of iodine-131. As a consequence of the charcoal disc, only very small amounts~~ ~~of iodine-131 (typically less than 1.85kBq (50nCi)) may be present in the packaging.~~ ~~containing one gigabecquerel is 5.7 x 10 -2 mSv/hr.~~ ~~The activity of a capsule at 12h00 GMT from calibration date~~	Partly accepted/amended: Product specifc data were deleted and replaced by <*Product specific additional information*>and the Table was left

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		~~can be calculated from the table 1.~~ ~~Table 1~~ ~~**Day** | **Coefficient** | **Day**~~ ~~-6 | 1,677 | 5~~ ~~-5 | 1,539 | 6~~ ~~-4 | 1,412 | 7~~ ~~-3 | 1,295 | 8~~ ~~-2 | 1,188 | 9~~ ~~-1 | 1,090 | 10~~ ~~0 | 1,000 | 11~~ ~~1 | 0,917 | 12~~ ~~2 | 0,842 | 13~~ ~~3 | 0,772 | 14~~	
Section 11 Line 622		Comment: Replacement of "mass" by "volume" according to section 4.2 Proposed change (if any): The activity might then be adjusted according to thyroid ~~mass~~**volume**~~ ~~, biological half-life and the "re-cycling" factor which takes into account the physiological status of the patient (including iodine depletion) and the underlying pathology	Accepted/amended
Section 11 Line 626 and following		Comment: Use same terminology as in section 4.2 (lines 136 and following) Proposed change (if any): ~~Unique nodule~~ unifocal autonomy:Target organ dose 300 –	Accepted/amended: additionally added Morbus Basedow in brackets

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		400 Gy ~~Multiple or disseminated~~ ~~nodules~~multifocal and disseminated autonomy :Target organ dose 150 – 200 Gy ~~Basedow~~ Graves' disease : Target organ dose 200 Gy	
Section 11 Line 610 till 644		Comment: values in table should be updated according to ICRP 128	Accepted/amended
SPC Section 12 Line 646 till 651		Comment:Guideline on CoreSPC for Radiopharmaceuticals *[Section 12 is designated to describe the dilution of a ready-to-use (multidose) radiopharmaceutical or the reconstitution of a kit for radiopharmaceutical preparation with the eluate of a generator containing the radionuclide.* Proposed change (if any): **12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** ~~The capsules are ready for use. Determine the activity before use.~~ ~~<Any unused medicinal product or waste material should be disposed of in accordance with local requirements.>~~ **Not appropriate**	Accepted/amended in modified form, redundancy was deleted.
PIL Line 404		Comment: Typing error Proposed change (if any): How ~~**to**~~ X is used	Amended

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PIL Section 1 Line 711		Comment: Annotated EMA QRD Template Version 10 [Invented name, active substance(s) and pharmacotherapeutic group] [You should first of all include the invented name of the medicinal product and the active substance(s) included in it, if necessary, as per section 1 and 2 of the SmPC, e.g. "X contains the active substanceY". Proposed change (if any): **1. What X is and what it is used for** X contains the active substance sodium iodide-131. This medicine is a radiopharmaceutical product for therapy only.	Accepted/amended
PIL Section 2 Line 730 to 736		Comment: friendly wording Proposed change (if any): **X must not be used,** if you are - allergic to sodium iodide or any of the other ingredients of this medicine (listed in section 6) - pregnant or breast-feeding if you have - swallowing problems - obstructed gullet - stomach problems - reduced abdominal or bowel movement If any of these apply to you, **tell your nuclear medicine**	Accepted/amended

		doctor.	
PIL section 2 Line 737 and following		Comment: Information should be given to patients with bladder voiding problems, and patients with digestive or stomach problems, and to patients with exophtalmy. Proposed change (if any): Inform the nuclear medicine doctor: - if you have reduced kidney function. • If you have bladder voiding problems, • If you have digestive or stomach problems • If protruding eyes are part of the symptoms of the disease you are suffering from (Graves' disease-induced ophthalmopathy) **If any of these apply to you, talk to your nuclear medicine doctor**. X may not be suitable for you. Your nuclear medicine doctor will advise you.	Accepted/amended
PIL Section 2 Line 739		Comment: redundant information, posology should be given in section 3 and precautions under the healthcare personnel is given in section 5. Proposed change (if any): ~~X is given in one single dose by specialists, who will take responsibility for any necessary precautions.~~	Accepted/amended in modified form: *X is given as one single capsule by specialists, who will take responsibility for any necessary precautions.*
PIL Section 2 Lines 743 to 747		Comment: wrong wording for therapy Proposed change (if any): **Before administration of X you should** - drink plenty of water before the start of the ~~examination~~ procedure in order to urinate as often as	Accepted/amended

		possible during the first hours after administration. - be fasting.	
PIL Section 2 Line 750		Comment: Additional information. Proposed change (if any): **Children and adolescents** Talk to your nuclear medicine doctor if you are under 18 years old or if you cannot swallow a capsule whole.	Accepted/included
PIL Section 2 Lines 752 and765		Comment: Missing information (SPC 4.5) Proposed change (if any): **Other medicines and X** Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription. c) **cortisone:** medicines to reduce inflammation or prevent organ transplant rejection for 1 week	Accepted/included
PIL Section 2 Line 788		Comment: Information on low iodine diet Proposed change (if any): **X with food** Your doctor may recommend a low iodine diet prior to therapy and may ask you to avoid foods such as shellfish and crustaceans .	Accepted/included

PIL Section 2 Line 789 to 796		Comment: Guideline on CorePIL for Radiopharmaceuticals Proposed change (if any): **Pregnancy and breast-feeding** If you are pregnant or breast-feeding, or think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine. **You must inform** the nuclear medicine doctor **before** the administration of X : - if ~~there is a possibility~~ you might be pregnant, - if you have missed your period or - if you are breast-feeding. ~~When in doubt,~~ If you are in any doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure. ~~As a precaution, men should not father a child for a time period of 6 months after radioiodine treatment~~ (already specified LINE 800)	Accepted/amended, redundancy was deleted.
PIL Section 2 Line 797		Comment:Guideline on CorePIL for Radiopharmaceuticals Proposed change (if any): **If you are pregnant** **Do not take** X if you are pregnant. Any possibility of pregnancy must be ruled out before using this medicine. **You must inform the nuclear medicine doctor before the administration** if there is a possibility you might be pregnant or if you have missed your period.	Accepted/amended

PIL Section 2 Line 799 and 803		Comment: Missing Contraception title and Fertility subsection Proposed change (if any): **Contraception in males and females** Women should not become pregnant until at least 6 – 12 months after using X. Women are advised to use contraception for a time period of 6 -12 months. As a precaution, men should not father a child for a time period of 6 months after radioiodine treatment to allow the replacement of irradiated by non-irradiated spermatozoa. **Fertility** Reproduction capacity may be affected transiently in men and women after treatment with XX. In men, high doses of sodium iodide (^{131}I) may affect **sperm production** temporarily. If you would ever like to father a child, speak to your doctor about whether saving your sperm in a sperm bank should be considered.	Accepted/included
PIL Section 2 Line 804		Comment: Missing information Proposed change (if any): **If you are breast-feeding** Tell your doctor if you are breast-feeding because you should **stop breast-feeding 8 weeks before treatment. Breast-feeding should not be resumed** Moreover mother or father, you must avoid close contact with your baby for a few days. Your nuclear medicine doctor will inform you of the number of days.	Accepted/amended in modified form, Because of redundancy the sentences *Moreover mother or father, you must avoid close contact with your baby for a few days. Your nuclear medicine doctor will inform you of the number of days*. were not included.

PIL Section 2 Line 815		Comment: Missing alternative Proposed change (if any): <u>< X contains less than 23 mg of sodium per capsule, i.e. essentially 'sodium- free'.</u>	Accepted/included
PIL Section 3 Line 829and 835		Comment: - Friendly term - Redundancy Proposed change (if any): 200-800 MBq (MBq = megabecquerel, the unit used to express radioactivity) to treat overactive thyroid gland; ~~MBq is the unit used to measure radioactivity and defines the activity of a quantity of radioactive material.~~	Accepted/amended in modified form, redundancy was deleted.
PIL section 3 Line 841		Comment: Missing information Proposed change (if any): **Administration of X and conduct of the procedure** <u>X is given in one single dose</u> <u>Your stomach should be empty when taking this capsule.</u> Healthcare professionals will give you the capsule….	Accepted/amended in modified form, redundancy was deleted.
PIL Section 2 Line 850		Comment: Missing information Proposed change (if any): **After administration of X, ~~you should~~** ~~avoid any close contact with infants and pregnant women for an appropriate period of time~~ ~~- urinate frequently in order to eliminate the medicine from your body~~	Not accepted/amended in modified form: *The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Particularly, you* - *must avoid any close contact with infants and pregnant women for for a few days. Your nuclear medicine doctor will inform you of the number of days.* - *should drink plenty of fluids and urinate*

		The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. These include: • **Avoiding any close contact** with infants and pregnant women for an appropriate period of time • **Drinking plenty of fluids** to ensure **frequent urination** in order to eliminate the product from your body • **Flushing the toilet carefully after** use and wash your hands thoroughly as your **bodily fluids** will be radioactive • **Having drinks or sweets that contain citric acid** e.g. orange, lemon or lime juice to help produce saliva and stop swelling of your saliva glands. • **Having specific laxatives** that stimulate the bowel, if you have less than one bowel movement a day. Also your blood, stools, urine or possible vomit are considered radioactive and should not come into contact with other people. Contact your nuclear medicine doctor if you have any questions.	*frequently in order to eliminate the medicine from your body* - *-should flush the toilet carefully and wash your hands thoroughly as your bodily fluids will be radioative* - *should have drinks or sweets that contain citric acid e.g. orange, lemon or limejuice to help produce saliva and stop swelling of your saliva glands* - *should have specific laxatives that stimulate the bowel, if you have less than one bowel movement per day.* *Your blood, stools, urine or possible vomit are considered radioactive and should not come into contact with other people.* *Contact your nuclear medicine doctor if you have any questions.*
PIL Section 4 Line 866		Comment: Redundancy with information in section 1 Line120 Proposed change (if any): Like all medicines, this medicine can cause side effects, although not everybody gets them. ~~Your doctor has considered that the clinical benefit that you will obtain from the procedure with X overcomes the risk due to radiation.~~	Accepted/ redundancy was deleted

PIL Section 4 Line 893 and 939		Comment: According to the SPC section 4.8, it has been added "Congenital hypothyroidism" in the SOC Congenital, familial and genetic disorders in the table "Adverse reactions after treatment of benign disease", therefore the PIL is amended accordingly. Proposed change (if any): **Treatment of non-cancerous diseases** **Frequency not known**, frequency cannot be estimated from the available data – …… – reduction or loss of parathyroid hormone production with tingling in the hands, fingers, and around the mouth to more severe forms of muscle cramps - Congenital thyroid hormone deficiency **Treatment of cancers** **Frequency not known,** frequency cannot be estimated from the available data – congenital thyroid hormone deficiency	Accepted/amended
PIL Section 4 Line 925		Comment: addition of a missing information according to SPC Proposed change (if any): **Treatment of cancers** **Frequency not known,** frequency cannot be estimated from the available data - …….	Accepted/amended

		– reduction or loss of parathyroid hormone production, increase of parathyroid hormone production	
PIL Section 4 Line 944		Comment: Missing information Proposed change (if any): **Reporting of side effects** If you get any side effects, talk to< the nuclear medicine doctor>, your <doctor> <or> <,> <pharmacist> <or nurse>.	Accepted/amended
PIL Section 4 Line 957		Comment : This could be presented as optional since this information intended for healthcare professionnals only, can be given in the SPC provided in the packaging (as written at the end of the PIL) Thus it is useful to delete storage conditions for readability reason. Proposed change (if any): **≤**The following information is intended for the specialist only. X must not be used after the expiry date which is stated on the label after 'EXP'**.≥**	Accepted/included
PIL Section 6 Line 977 to983		Comment: Missing information Proposed change (if any): <Detailed information on this medicine is available on the website of {name of MS Agency (link)}> The following information is intended for medical or healthcare professionals only: The complete Summary of Product Characteristics (SmPC) of X is provided ~~as a separate document~~ <as a separate	Accepted/included

		document> <as a tear-off section at the end of the printed leaflet> in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical. Please refer to the SmPC ~~of X~~.	

Please add more rows if needed.

[i] Royal College of Physicians. Radioiodine in the management of benign thyroid disease: clinical guidelines. Report of a Working Party. London: RCP, 2007.

[ii] Stokkel MPM, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. Eur J Nucl Med Mol Imaging 2010; 37: 2218-28.