



Methods for preparation and administration of lutetium-177 oxodotreotide 3.7 GBq: proceedings from an Italian advisory board

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Lutetium-177 (¹⁷⁷Lu)-oxodotreotide (Lutathera[®]) is a targeted radiolabelled somatostatin analog approved for metastatic or unresectable, well-differentiated (G1 and G2), progressive, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [1]. Oxodotreotide has high affinity for somatostatin subtype 2 receptors, which are overexpressed by most GEP-NET cells but have low expression in normal tissues [1, 2]. ¹⁷⁷Lu-oxodotreotide binds to these receptors and is internalized, thus delivering ionizing radiation more specifically to tumor cells than surrounding cells. In the phase 3 NETTER-1 study, ¹⁷⁷Lu-oxodotreotide plus long-acting octreotide low-dose (30 mg; for symptom control) significantly improved progression-free

survival and response rates compared with long-acting octreotide high-dose (60 mg) alone [3].

¹⁷⁷Lu-oxodotreotide is supplied in a single-dose vial (370 MBq/mL; expected radioactivity at infusion: 7.4 GBq; total vial volume: 20 mL), which is administered by infusion every 8 weeks for four administrations [4, 5]. Adverse reactions (including Grade ≥ 2 thrombocytopenia, Grade ≥ 3 anemia or neutropenia, renal toxicity, hepatotoxicity, or any other Grade 3 or 4 toxicity) can be managed by an increase in infusion interval to up to 16 weeks and, if the toxicity resolves during this time, treatment can be continued with the radioactivity reduced (halved) to 3.7 GBq [4, 6].

Because only the full-dose vial is available, when radioactivity is halved there is a risk of radiation exposure [7]. Furthermore, it is extremely important to identify methods for precise halving of the radioactivity, as approximations could be harmful for both the patient and staff members. The budgetary implications of radioactivity halving remain to be determined. Although theoretically the radioactivity remaining after halving can be used for another patient, saving the remainder may affect sterility or result in dose decay, and given the rarity of GEP-NETs, it is unlikely that two patients will require a half-dose at similar times. Additionally, the cost of the entire vial is used for reimbursement purposes, so the drug cost remains the same even when the radioactivity is halved.

There are currently no guidelines on radioactivity halving. Here, we report the findings of an advisory board meeting of Italian experts (two nuclear medicine physicians, five medical physicists and three radiopharmacists) who discussed possible approaches to halving ¹⁷⁷Lu-oxodotreotide radioactivity, with the aim of summarizing the risks and advantages of different methods and providing a basis for developing formal guidelines for Italy. While the advisory board agreed that deferring until a full dose can be administered safely is always preferred, it was recognized that there are some clinical situations in which radioactivity halving is

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the most suitable option, in particular in patients who experience the adverse reactions described above [e.g., to comply with the approved product information in accordance with Italian Medicines Agency (AIFA) regulations]. It is, therefore, important to develop a set of practical recommendations for radioactivity halving that can be used by nuclear medical centers and that can accommodate differing levels of material, economic and professional resources available between centers.

Possible methods of dose halving and administration: the prescribing information for ^{177}Lu -oxodotreotide gives specific instructions for the administration of the full 7.4 GBq radioactivity (Fig. 1) [5].

Reducing the infusion duration is one way to halve the dose. However, this method does not address the fact that the infusion rate is not linearly correlated with ^{177}Lu -oxodotreotide's radioactivity, making it difficult to achieve a precise measurement because of changes in the drug concentration during dilution and infusion.

Manual halving of ^{177}Lu -oxodotreotide is quick and easy to implement and can be achieved using the same

administration method as the full dose. One disadvantage is the risk of staff radioactivity exposure. Care must also be taken when inserting needles into the vial, because if the diameter of the hole created is too large, the vial will be rendered unusable. The authors agreed that any issues related to preserving the sterility of the manipulated product are negligible. Preparation of the radiopharmaceutical and measuring the residual radioactivity must always be performed under a laminar flow hood. In practice, two needles should be used, a short vent needle and a long aspiration needle. The half radioactivity should be aspirated into a syringe, the two needles must be covered with needle caps and the vial with the residual preparation handed to the physician for the infusion. The effective and equivalent doses of exposure for the worker when manually splitting the dose have been estimated. Using a gamma ray dose constant of $0.00517 \mu\text{Sv m}^2/\text{MBq h}$ [8], an unshielded worker who spends 3 min splitting ^{177}Lu -oxodotreotide (at a distance of 10 cm for the hands and 50 cm for the body) will be exposed to an effective dose of $7.7 \mu\text{Sv}$. When shielded (body, 2 cm lead), the calculated effective dose drops to $0.19 \mu\text{Sv}$. Using the same

Gravity infusion method for Lutathera administration

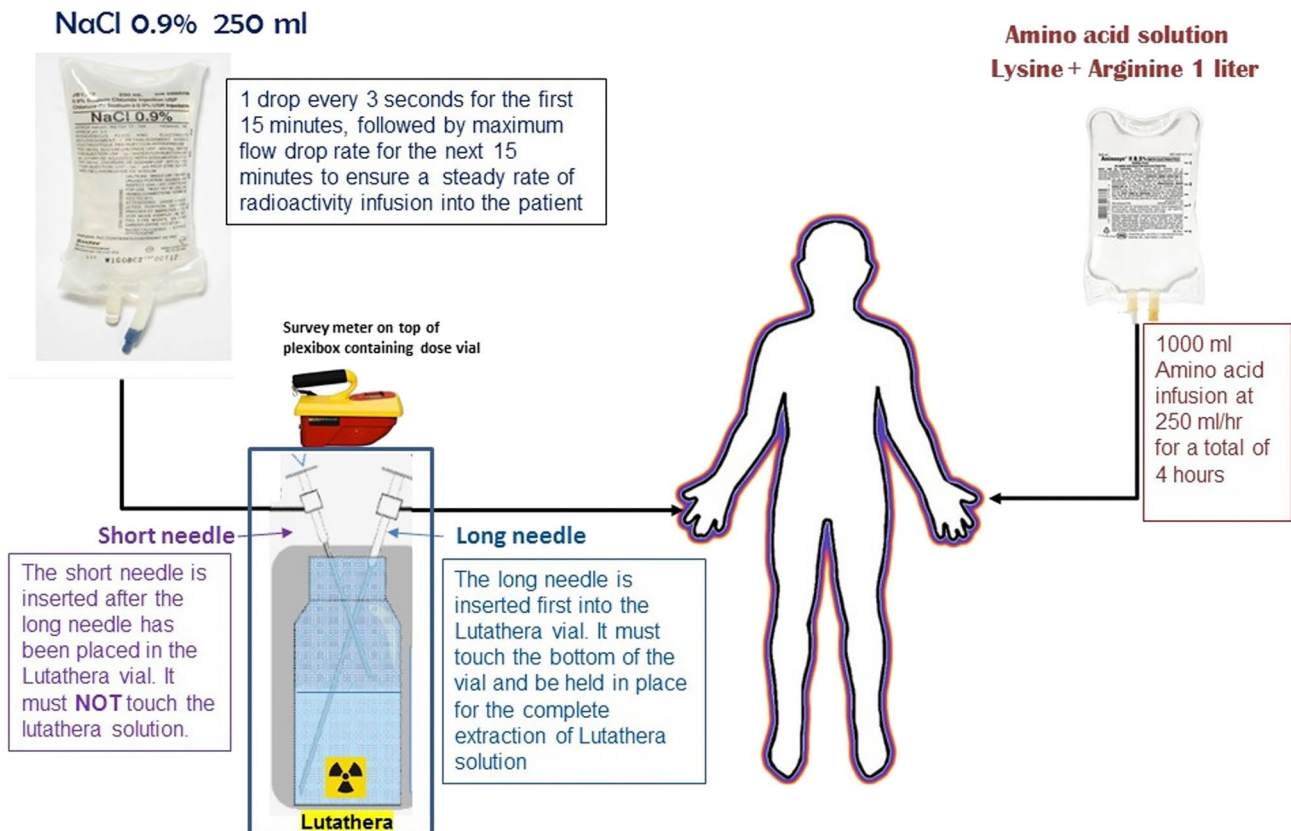


Fig. 1 Recommended gravity infusion method for administration of ^{177}Lu -oxodotreotide. Reprinted from Journal of Radiology Nursing, 38, Lora K. Hromadik, Laura Sturges, Caring for patients receiving

^{177}Lu -DOTATATE, Lutathera[®]: a treatment of hope for patients with gastroenteropancreatic neuroendocrine tumors, 28–32, Copyright (2019) with permission from Elsevier

methodology, the calculated equivalent dose to the hands of workers was 0.19 mSv when unshielded and 0.00008 mSv when shielded. The specific gamma ray dose constant of ^{177}Lu is markedly lower than that of some other commonly used isotopes (e.g., ^{131}I iodine, ^{18}F fluorine, $^{99\text{m}}\text{Tc}$ technetium). Thus, the board agreed that the exposure risks to the personnel performing the halving are extremely low.

An automated fractionator is a practical way to split radioactivity while minimizing exposure. However, there is still the risk of exposure when the radiopharmaceutical is removed from the equipment and when it is administered. The automated fractionator needs to be specifically calibrated for measuring lutetium radioactivity, but vendors of these machines do not currently provide certification for this. Additionally, different fractionating machine models use different measures and infusion syringes, and the availability of suitable infusion kits also varies. It is therefore difficult to provide standardized recommendations for radioactivity halving using an automated fractionator. Other disadvantages are the potential for contamination of the machines after use due to human error, and unavailability of these units at many centers.

Continuously monitoring radioactivity during infusion and stopping the infusion once the dose rate is half of the initial rate is another option. This has the advantage of eliminating personnel exposure, but is limited by the major imprecision of measurement.

Alternative administration methods for halved radioactivity: use of an intravenous drip to administer a half-dose of ^{177}Lu -oxodotreotide has been suggested. The halved radioactivity is transferred from the vial to a saline-containing drip bottle and then administered to the patient. Disadvantages include increased exposure for personnel, as the radioactivity in the drip bottle would not be shielded (unlike the traditional method where the radioactivity is contained within the vial shield). The personnel transferring the halved activity to the drip bottle would also be exposed. Using the same values for effective dose rate constant and distances from hands and body as mentioned above, a shielded staff member who spent 2 min transferring ^{177}Lu -oxodotreotide from the vial to the drip bottle would be exposed to an effective and equivalent dose of 0.07 μSv and 0.00003 mSv, respectively.

An infusion pump can also be used to administer ^{177}Lu -oxodotreotide after manual halving. However, this method still results in personnel exposure during halving, as the required radioactivity must be drawn into a syringe. Infusion pumps are generally not shielded, also causing exposure. As such, total exposure during preparation plus administration may be greater than manual halving followed by standard administration.

Further action: it is unlikely that pre-packaged ^{177}Lu -oxodotreotide 3.7 GBq vials will become commercially

available because their infrequent use would preclude the financial investment required to obtain registration. The board agreed that the manual halving method should be further investigated and refined because it can be implemented in most centers with minimal re-training, and that a set of guidelines regarding options for the preparation and administration of ^{177}Lu -oxodotreotide 3.7 GBq be prepared. To this end, the experts agreed to further action, supported by the manufacturer, including testing of the validity and flow of the product from the vial after subtraction of a given quantity, and identification of a standard needle size to administer ^{177}Lu -oxodotreotide 3.7 GBq.

In conclusion, although half-doses of ^{177}Lu -oxodotreotide are used relatively infrequently, it seems important to have a set of procedural recommendations for their preparation and administration. Manual radioactivity halving was identified by the advisory board as the most suitable method for further development.

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Authors' contributions MA attended the advisory board supporting the discussion on the technical approach to be adopted. He performed practical tests using the manual halving method with both non-radioactive liquids and the radiopharmaceutical solution. He has read and approved all drafts of the manuscript. LD participated in the discussion of the advisory board with regard to technical and radiation protection assessments, and has read and approved all drafts of the manuscript. VDI participated in a discussion of the methods to use for the advisory board with a focus on assessments of a radioprotective and pharmaceutical nature, and has read and approved all drafts of the manuscript. MF attended the advisory board, supported the work group with regard to technical and radiation protection assessments, and has read and approved all drafts of the manuscript. AF attended the advisory board and supported the work group by participating in the discussion on the technical approaches and radiation protection. She attended the execution of practical tests on the manual halving methods and adopted the results obtained in clinical practice. She has read and approved all drafts of the manuscript. GG participated in the discussion of the methods to use for the advisory board with a focus on assessments of a radioprotective and pharmaceutical nature, and has read and approved all drafts of the manuscript. MM was involved in content planning and editing of the manuscript, and has read and approved all drafts of the manuscript. CP attended the advisory board, supported the work group with regard to technical and radiation protection assessments, and has read and approved all drafts of the manuscript. MS attended the advisory board, supported the work group with regard to technical and radiation protection assessments, and has read and approved all drafts of the manuscript. AZ attended the advisory board, supported the work group with regard to technical and radiation protection assessments, and has read and approved all drafts of the manuscript.

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Declarations

Conflict of interest Mattia Asti, Laura D'Ambrosio, Valentina Di Iorio, Mahila Ferrari, Angelina Filice, Giancarlo Gorgoni, Marco Maccauro, Cinzia Pettinato, Michele Stasi and Alessandra Zorz all received honorarium from AAA for advisory board participation. However, this paper reflects the independent views of the participating Italian health-care professionals.

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