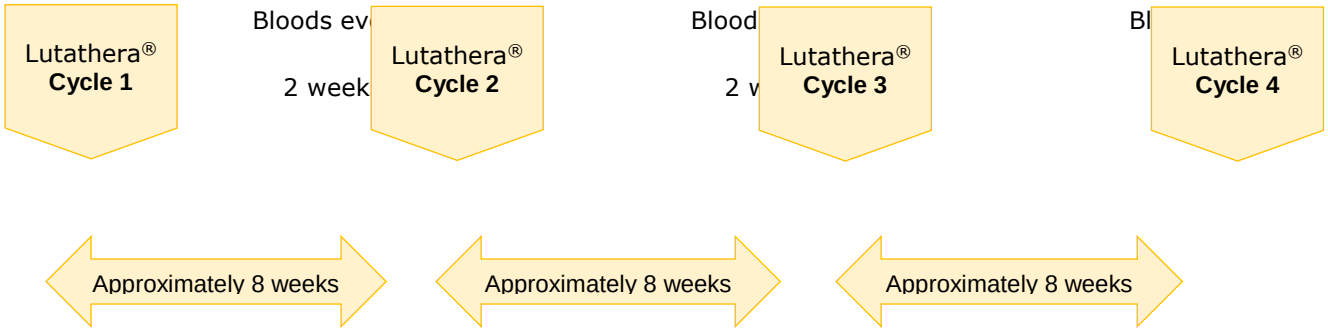
Detailed Information about PRRT

Introduction:

Peptide Receptor Radionuclide Therapy (PRRT) is a treatment for neuroendocrine cancer. This leaflet explains why PRRT is being considered for you, what is involved and the benefits and risks of the treatment.

What is PRRT (lutetium (^{177}Lu) oxodotreotide (Lutathera®))?

- **P**eptide **R**eceptor **R**adionuclide **T**herapy or **PRRT** is an approved treatment for neuroendocrine tumours. PRRT delivers radiation therapy directly to any tumours in your body that are visible on your DOTATOC PET/CT Scan.
- The type of PRRT that has been recommended for you is called Lutathera®.
- The procedure consists of four treatments (infusions) ideally given about eight weeks apart and may be increased to up to 16 weeks if you have certain side effects. In general, the first infusion will require an overnight stay in hospital and the remaining three infusions may be given as an out-patient.
- Between each infusion, you will be contacted by the nurse specialist/ doctor to review how the treatment is working for you. You will also have regular blood tests to ensure it is safe for you to proceed to the next treatment.
- To protect other people from the radiation you have been given, you will be asked to take some precautions for 2-3 weeks after each treatment.
- The treatment procedure and the required precautions are discussed in detail in this information leaflet.



Why is this treatment being considered for me?

You may have already had other treatments, including chemotherapy or surgery. These treatments may no longer be effective on your cancer. PRRT is an internationally well recognised and used treatment for neuroendocrine cancer. A team of specialist doctors have decided to offer you this treatment as they feel it is the best option for you. In making their decision, the doctors will have considered your general health and a range of diagnostic tests, including special imaging investigations.

How does it work?

Some neuroendocrine cancer cells have proteins (receptors) on the outside of them called somatostatin receptors. Lutathera® works by specifically targeting these receptors with a drug containing somatostatin (a hormone) and Lutetium-^{177} (a radioactive substance). When injected into the bloodstream, the hormone somatostatin attaches to these receptors and the Lutetium-^{177} then enters the cancer cells and releases radiation that destroys the cells from the inside. By delivering a high, radiation dose directly to cancer cells, PRRT minimises the damage to surrounding healthy cells.

Before being considered for PRRT you will have had a Gallium PET-CT scan to check whether the neuroendocrine cancer cells in your body have these somatostatin receptors. If these scans show that they do, they can be targeted with Lutathera®.

How can I benefit from this treatment?

Since every patient is different, it is difficult to predict exactly how much you may benefit from this treatment. Lutathera® is one of the only effective treatments for inoperable neuroendocrine cancer that has spread in the body. It cannot cure the cancer, but it can cause it to shrink, delay it spreading, and prolong life.

Lutathera® was assessed in a clinical trial called the NETTER-1 study. In this study, PRRT was compared with a high dose of a standard therapy (long-acting octreotide 60 mg) in patients with advanced-stage neuroendocrine tumours (NETs) of the small bowel or ascending colon. Results showed that -Lutathera® was 82% more effective in preventing tumour growth and spread. Lutathera® was also shown to significantly improve patients' quality of life, reducing pain, fatigue and diarrhoea. Further information about the NETTER-1 trial results can be found in the document listed in the references section.

Pre-treatment procedures and advice:

Before starting your course of PRRT, you will have a consultation with a PRRT nurse specialist and a Radiologist in the Nuclear Medicine department, who will explain the therapy procedure in detail. A physicist will also discuss with you the special precautions you will need to take after each therapy cycle. You will be provided with contact details of who to contact should you have any further questions following these initial consultations. On the same day as this consultation, you may also have some blood tests.

Medication:

It is important that any long-acting somatostatin analogue injections (such as lanreotide (Somatuline® LAR), ocreotide (Sandostatin® LAR), or Pasireotide (Signifor® LAR)), are stopped 4 weeks prior to PRRT and short acting somatostatin analogue injections are stopped 24 hours prior to PRRT. This is because these drugs may block the receptors that the therapy is designed to target and therefore potentially reduce the success of the treatment. HOWEVER, THE REFERRING NET CONSULTANT WILL DECIDE WHTEHER YOU SHOULD STOP THESE INJECTIONS OR NOT BEFORE PRRT TREATMENT.

Your NET consultant will have already have discussed this with you, and your PRRT appointments should have been timed to coincide with your monthly injections. If not, please get in touch with the Nuclear Medicine Department. If necessary, you may be switched to short-acting somatostatin analogues, which need to be discontinued 24 hours before the planned therapy.

Pregnancy / Breastfeeding:

Lutathera® will continue to release radiation for several weeks but the radiation levels will decrease constantly during that time. The radioactivity will have disappeared almost completely after about one month. However Lutathera® can cause harm to an unborn child if given to a pregnant woman and we do ask you:-

- Not to become pregnant or induce pregnancy during your entire treatment and for 6 months after your last infusion.
- Stop breastfeeding prior to starting treatment.

It is advisable that women of child bearing age use effective contraception during the treatment and for 6 months afterwards and that men with partners of child bearing age use effective contraception during treatment and for 6 months afterwards.

Please note that the radiopharmaceutical is ordered specially for your treatment and has to be used immediately. Therefore, it is

important that you inform us at least TWO WEEKS in advance if you are unable to attend for the treatment.

Procedures on the day of your treatment:

On the day of your first infusion you will attend Admissions in St. Vincent's University Hospital (SVUH) and will be directed to St Lucy's ward (Herbert Wing). From there you will be brought to the Nuclear Medicine therapy room.

For your second and consecutive treatments if you are being treated as an outpatient you will attend the Nuclear Medicine department directly on the day of therapy. The time of attendance at SVUH will be confirmed in your appointment letter.

In the Nuclear Medicine therapy room the Radiologist will explain the details of the treatment to you and you will be asked to sign a consent form to show that you agree to the treatment.

Before the treatment you will be changed into a hospital gown. The PRRT nurse will insert a needle into a vein on each arm. Blood tests may be taken if needed at this point. You will also be given some anti-sickness medication to reduce the side-effects of nausea and vomiting during the infusion.

Amino acids will be given to you through the needle; this will last for about four hours in total. The amino acids help protect your kidneys from being damaged by the radiation. Approximately one hour after starting the amino acid drip, the Lutathera® will be given to you through the other needle.

Because Lutathera® is radioactive; staff will wear aprons, gloves and overshoes, and use special equipment to protect them from the radiation. Once the Lutathera® has been administered you will become a source of radiation to others, so staff will remain at a distance from you whenever possible. This will not affect your care and you will be closely monitored at all times.

The Medical Physics team will also make measurements of the radioactivity in your body during and after the Lutathera® infusion.

Before, during and after the Lutathera® is given, your blood pressure and heart rate will be monitored. After you have received the Lutathera®, you must remain in the therapy room for several hours for observation until the amino acids are finished.

Once the observation time is complete, you will be brought to St. Lucy's ward if it is your first treatment, or if it is your second or subsequent treatment you may be able to return home.

Procedures on the day after your treatment

After your first infusion you will return to the Nuclear Medicine department on three separate days ideally, within the first week, for scans. The first scan will be performed the day after your therapy. The timing of the other scans will depend on what day you have your infusion. This will be discussed with you at the time of your initial consultation. On the remaining cycles you will attend the Nuclear Medicine department for a single scan. You will also see the Medical Physicist after each scan, who will make a measurement of the external radiation. These scans will tell the doctor how much radiation is in the tumours and normal organs.

Procedure between each infusion

Between infusions of PRRT, you will have blood tests every two weeks to check your blood, liver and kidney function. This can be done with your GP or at your local hospital and we will give you contact details of how to send on the results to SVUH. The NET team will receive and monitor these blood results. In the event that your blood count falls significantly, we may need to delay the next infusion of PRRT, refer you for additional procedures (such as a blood transfusion) or reassess your treatment plan. You will also have a CT or MRI scan between your second and third infusions to monitor your disease.

Procedure after the last cycle

After you have received four infusions of PRRT, you continue to have blood tests every two weeks for eight weeks and you will be followed up by your NET consultant, who will refer you for a CT or MRI scan to assess your response to therapy.

Reducing radiation to other people:

For the first few weeks after each Lutathera® treatment a small amount of this radiation is constantly coming out of your body, so people in contact with you will be exposed to this radiation.

Will there be any danger to my family or others?

No as the radiation levels are very low, however we do ask you to take some simple precautions. These precautions are to avoid additional radiation exposure to your family and others above that which they are exposed to on a daily basis from natural background radiation. Further information on background radiation in Ireland can be found at:

https://www.epa.ie/environment-and-you/radiation/radiation-exposure-and-your-health/your-radiation-exposure/

The easiest way to avoid additional radiation exposure to someone is to reduce your time spent in close contact with them, for example, do not sit close to a person if there is a seat available further away. The following precautions and instructions should be followed for the duration stated.

Day of therapy – your stay in the hospital:

During your stay in the hospital you will be asked to drink lots of fluids and use the toilet often (ideally once an hour) to flush any excess radioactivity from your body. We also recommend that you shower in the evening of the first day, and again the following morning.

For your first treatment you will stay over-night in a single room in St. Lucy's ward. The room has its own toilet, shower, TV and has WiFi. The room will have been pre-prepared with some surfaces covered with a protective film and absorbent pads. This is because, after the Lutathera® is given, your body fluids, such as urine, will be slightly radioactive, and covering some surfaces helps us to prevent radioactive contamination in the room. If you are being treated as an outpatient you will be monitored in the Nuclear Medicine department for a few hours after your infusion before going home.

Advice for when you leave hospital:

At home 	**For the first week after therapy:** • Shower or bathe every day. • Continue to use the toilet often and sit while urinating. • Flush down the toilet any tissues containing bodily fluids like blood, urine and faeces. • Try to pass stool every day, use a laxative if you need to. • Wash your hands well with soap and water after using the toilet and after any contact with bodily fluids. • Wash your underwear, pyjamas, sheets, and any clothes that contain sweat, blood, or urine separately from the laundry of other members of your household, using a standard washing cycle. You do not need to use bleach and do not need extra rinses. • If you have loose stools or urinary incontinence use protective underwear or incontinence pads. This helps prevent contamination of clothing and your home. Place used underwear / pads in a plastic bag and store outside in an un-occupied area for 70 days before throwing out in the normal bin.
Travelling Home 	• If you need to arrange for assistance in getting home it is preferable that you travel by private transport, and that you sit diagonally opposite the driver i.e. in the back seat, ensuring no other passengers are in the vehicle.
Transport 	• Public transport should be avoided on the day of treatment. Journeys less than one hour are permitted from day 2 onwards. Journeys from 1 – 2 hours are OK from day 3 onwards and journeys of 2 – 3 hours are OK from day 5 onwards.
Contact with your spouse /partner 	• To reduce the radiation dose to your partner it is recommended that you sleep in separate beds for the first 14 days after treatment. • During the day contact should be limited to no more than 2.5 hours at distance of 2m for the first week, and no more than 5 hours per day at 2m for the second week. • For the third week daytime contact should not exceed 6 hours at 1m but contact at distances greater than 1m is OK.
Contact with other adults 	• To reduce the radiation dose to other adults, whom you do not live with, avoid contact within 1 metre for the first 7 days. In the second week you should not spend more than 1 hour per day at a distance of 0.3 m (arm's length distance). Being in their company at distances greater than this is OK.

Pregnant women/ children 	• It is better to have **no** contact with young children (< 11 years old) or pregnant women for the first 7 days after treatment. You should avoid close contact (keep to <1 hour per day at 0.3 m) during the second and third week after therapy. Limited contact at greater distances is OK. • Sleep apart from pregnant women or children for the first three weeks. • Specific advice can be given based on the age of your children.
Contact with over 60's 	• Provided you stay more than an arm's length away from those over 60 years of age in the first 2 weeks, there are no additional restrictions required.
Contact with Family Member caring for you 	• It is possible for an adult family member to look after you before the time periods stated have passed, if you are unwell or disabled for example, provided they are not pregnant. • If your partner or other family member is in this position, he/she may receive a higher radiation dose as a result of looking after you, and must be aware of the small risk involved. **<u>Please ask them to attend your initial consultation with you, and the medical physicist will explain the various risks and precautions involved.</u>**
Contact with Pets 	• There is no evidence to suggest that your pet's health will be at risk after your treatment and you do not need to avoid contact with them.
Places of Public Entertainment 	• Such as theatres, cinemas, bars should be avoided in the first 5 days after each treatment.
Returning to Work 	• If working in close contact with adults (within 0.3 metre of the same person for more than 8 hours per day) you should stop working for the first 7 days after each treatment and ensure the distance to your co-workers is greater than 1 metre for the following 2 weeks. • If working with young children or pregnant women you will have to take additional time off work.
Travel 	• If you plan to travel abroad in the 3-month period following treatment, please notify the medical physicist and they will give you a letter indicating that you have had Lutathera® treatment.

What should I bring to hospital with me?
For your inpatient ward stay you are welcome to bring any belongings with you, but please be aware that they must be monitored for radioactivity before you leave. It may be necessary for us to keep any radioactive belongings for a period of time after you have left the hospital. For this reason we recommend bringing the minimum amount of belongings possible. You will be able to collect any of your belongings we keep from the Nuclear Medicine department after a few weeks.
Items that are useful to bring into hospital include snacks and drinks, pyjamas (very likely to be kept), slippers (may be kept), books/magazines (unlikely to be kept), mobile phone (will not be kept) and toiletries. Please bring a complete change of clothes to wear when you are discharged home.

Are there any side-effects from this treatment?

There are several possible side effects from the treatment procedure, some arising from the amino acids and some from the Lutathera®. Not all patients will experience these side effects. Detailed information about the side effects can be found on-line in the Summary of Lutathera® Product Characteristics (on-line address listed at the end of this document). The most common side effects are listed below. A side effect is considered "very common" if they affect at least 1 in 10 patients, "common" if they affect at least 1 in 100 patients and "uncommon" if they affect at least 1 in 1,000 patients.

Short-term side effects:

- ***Tiredness.*** This is a very common but usually mild and may last for a few weeks after treatment.

- ***Nausea / vomiting / decreased appetite.*** Nausea and vomiting are very common during the treatment. You will be given anti-sickness medication before your treatment to help with this.

- ***Fall in blood count.*** This is very common and usually temporary, but could cause a delay in your next cycle of PRRT. A fall in blood count can leave you more prone to infection, bleeding and bruising or leave you feeling tired and short of breath. Your blood count will be checked before you start treatment and every 2 weeks while you are undergoing treatment. If you notice any bruising or bleeding it is important to contact PRRT specialist nurse or the NET team.. Some drops in blood count may require treatment with a blood transfusion.

- ***Diarrhoea.*** This is common but is usually mild and usually should not need any specific treatment.

- ***Abdominal Pain:*** Stomach pain is common and may last for a few days after treatment. If you have persistent or severe pain you should contact the PRRT specialist nurse or the NET team.

- ***Mild hair loss.*** This is common but usually minimal (much less than chemotherapy), and re-grows after the treatment has finished.

- ***Hormonal syndromes*****.** The treatment can cause a sudden release of hormones, resulting in so-called *"functional syndromes"* or *"neuro-hormonal syndrome"*, such as carcinoid syndrome, which vary depending on the type of hormone. Symptoms may include flushing, wheezing, increased heart rate and breathlessness. This is uncommon but if left untreated can result in a hormonal crisis. This is most likely to occur in the first 48 hours after your treatment. We will be monitoring you closely throughout your stay for any signs of this. If it occurs, we will give you additional medication to treat the syndrome, and we may need to keep you in hospital for longer than planned. If you develop any of these symptoms after you return home you should attend your closest emergency department and contact the PRRT specialist nurse or NET team.

- ***Tumour lysis syndrome*****.** Tumour cells can be destroyed quickly following Lutathera® infusion and uncommonly this results in tumour lysis syndrome which can cause an irregular heart-beat, kidney problems or seizures. If you develop any muscle cramps or weakness, confusion, or shortness of breath it is important to contact the PRRT specialist nurse or NET team and attend your nearest emergency department.

- ***Allergic reaction*****.** Allergy is uncommon and you will be monitored for this during and after your infusion.

Long-term side effects

- ***Impaired kidney function.*** This is common and in some cases patients have experienced kidney failure. The risk of this is minimised by giving you amino acids during the therapy. However, your kidney function will be checked before treatment and every two weeks during treatment, as well as routine monitoring after treatment.

- ***Impaired liver function.*** Patients with liver metastases may be more prone to impaired liver function. Your liver function will be checked before treatment and every two weeks during treatment, as well as routine monitoring after treatment.

- ***Blood cancer.*** Bone marrow disease also known as myelodysplastic syndrome of the bone marrow (usually a forerunner of leukaemia) and acute leukaemia has been noted in about 2% of patients. Your blood counts will be checked before treatment and every two weeks during treatment, as well as routine monitoring after treatment.

- ***Infertility.*** Treatment may cause infertility which can be temporary or permanent.

- ***Risk from radiation exposure.*** Lutathera® contributes to overall long-term radiation exposure. Cumulative radiation exposure is associated with increased risk of cancer. Every effort is made to minimise your radiation exposure and special precautions are provided below which will minimise your risk and your household contacts risk of exposure.

- ***Harm to an unborn child.*** Lutathera® can cause harm to an unborn child if given to a pregnant woman. It is advisable that women of child bearing age use effective contraception during the treatment and for 6 months afterwards and that men with partners of child bearing age use effective contraception during treatment and for 6 months afterwards. Breastfeeding must be stopped prior to commencement of therapy.

Other Considerations

In some cases it may be necessary to stay over-night as an in-patient for all four infusions of PRRT. If this is the case you will be informed of this by the NET consultant or radiologist.

When you are ready to go home, the medical physicist will give you a card with your treatment details on it. You will be required to carry this with you at all times for the time specified on the card.

In the unlikely event of death within the first few weeks after treatment, special precautions are required which will delay burial/cremation for up to a month. It is very important that the hospital is informed (via the contact numbers below), so that appropriate guidance may be given.

More information about this procedure can be obtained by contacting prrt@svuh.ie or:

Medical	***Radiation Protection***
Dr Nicola Hughes /	Ann McCann / Niamh McArdle
Dr Mathilde Colombie /	/ Jackie McCavana

Josh Nograles
Department of Radiology
Direct Tel.: 01 - 221 4463/3895 / 4409
Reception Tel.: 01 - 221 4992

Medical Physics Department
St. Vincent's University Hospital
Direct Tel.: 01 - 221 5278

Further Information about PRRT can also be obtained at:

NET Patient Foundation website:
http://www.neuroendocrinecancer.org.uk
Includes information, leaflets, news and a patient forum.

Summary of Lutathera® Product Characteristics: Available on-line at:
https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf

Academic paper about the NETTER-1 Clinical Trial:
Strosberg J, et al. Final overall survival in the phase 3 NETTER-1 study of lutetium-^{177}-DOTATATE inpatients with midgut neuroendocrine tumors 2021; 332-311. Available on-line at: https://pubmed.ncbi.nlm.nih.gov/34793718/