Training Healthcare Professionals (HCPs) on the safe management of intravenous (IV) treprostinil and the prevention of catheter-related bloodstream infections (CRBIs)

Medical Affairs Department
United Therapeutics Europe, Ltd

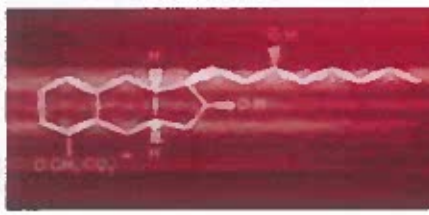
History

- For the safe management of treprostinil IV, the UT, in consultation with the regulatory authorities, has developed a "Risk Management Plan" (RMP) aimed at reducing the occurrence of catheter-related bloodstream infections (CRBIs)
- An information letter was developed for potential prescribers of IV treprostinil to alert them to the risks associated with this treatment.
- This set of slides, as well as the accompanying patient brochure and information letter, have been approved locally by the National Medicines Regulatory Agency.
- After a period of treatment with IV treprostinil, patients will be followed up with a specific "Patient Questionnaire" to confirm that risk management techniques have been understood and are being followed.
- If a bloodstream infection is suspected, it must be notified using the "Event of Special Interest" form.

Key points of this training session

- CRBI risk history
- Practical techniques for reducing CRBIs
- Remodulin SmPC
- Identification and reporting of suspected CRBIs, dosage errors and pump/infusion line malfunctions
- Transition from SC to IV treprostinil
- Abstract
- Suggested bibliography

The risk of catheter-related bloodstream infection (CRBI)



Pulmonary Hypertension Association: Bloodstream infection guidelines and catheter care

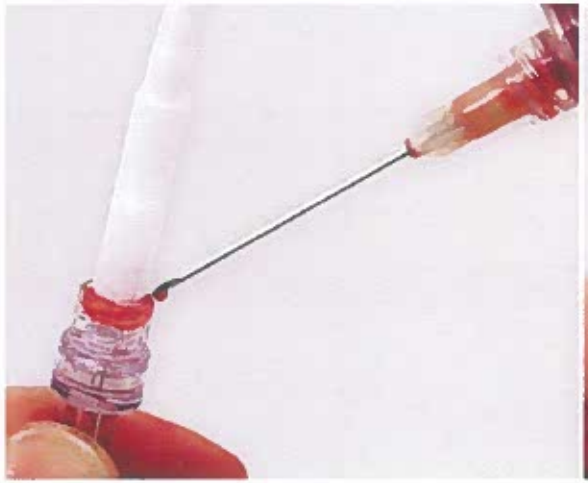
Possible infection gateways

- CVC cutaneous insertion site
- Catheter connection device and tubing connections
- Prostaglandin vials and reservoirs

BSI, bloodstream infection; BSI-CB, catheter-related bloodstream infection; CVC, central venous catheter

Entry of pathogens into the central venous line

Colourant enters the thread[1]



Contamination occurs when removing[2]

Connection covered with a plastic shield

1. Ivy et al. *Infect Control Hosp Epidemiol.* 2009;30:823-829; 2. Doran. Health Matters; Fall 2008. http://www.phassociation.org/Document.Doc?id=226. Accessed May 2010

Pulmonary Hypertension Association: Bloodstream infection guidelines and catheter care

Follow the Pulmonary Hypertension Association's guidelines for the prevention of CRBIs[1]

- Protection of catheter connector devices is essential
- Preventing contact with water is essential
- Pay attention to the type of skin insertion site dressing used and observe the site

BSI, bloodstream infection; BSI-CB, catheter-related bloodstream infection; CVC, central venous catheter

1. Doran et al. Adv Pulm Hypertens. 2008,7:245-248

Practical techniques for reducing CRBIs

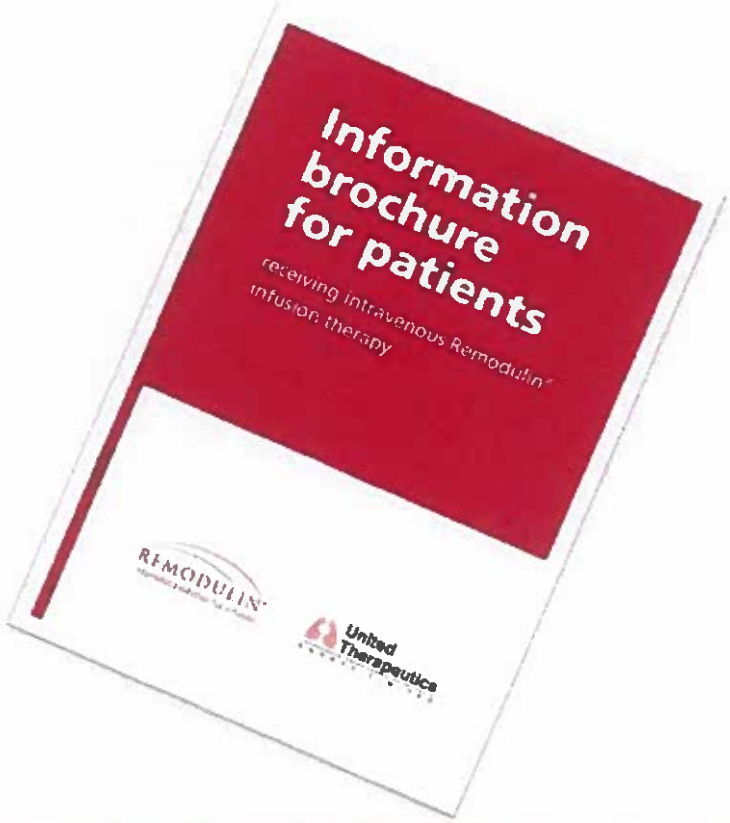
Patient instruction and essential general principles

- Patients must understand the risks associated with treatment, as well as the role they play in keeping them to a minimum. The medical team responsible must teach their patients:

  - **Hand hygiene** - the importance of correct hand washing with appropriate cleaning solutions and simple, effective techniques to maintain asepsis when preparing infusions
  - **Preparing the area** - the need to prepare the home environment thoroughly before changing the tank solution and pipework
  - **Maintenance and observation of** the catheter's skin insertion site and frequency of changing the gauze or transparent film covering
  - **The importance of keeping connecting devices dry** and the use of waterproof coatings or protections when showering or bathing. Swimming should be strongly discouraged
  - **The importance of keeping an eye out for signs and symptoms of** suspected CRBIs and informing a healthcare professional

Patient instruction and essential general principles

- An information brochure has been designed to help you explain these key points to the patient. After you have given them verbal instructions, it is important to check the patient's understanding of the brochure.



0.2 micron filter

- Eliminates bacteria, yeasts, moulds and foreign particles from the infusion line
- In a UT study, the catheter tubing was purposely contaminated to evaluate the filter's effectiveness
- In samples for pathogen culture of post-filter fluid, no evidence of contamination was observed [1]

1. Phares. Protocol: TTP-LRR-M00329. Data on file, United Therapeutics Corp

Split septum closed connector system

- The catheter connector is the most common source of central line infections[1,2]
- A split septum needleless device is preferable to a mechanical valve device. If a mechanical valve device is used, it must have a smooth, soft surface for pre-access disinfection[3]
- Closed connector devices give direct access to the fluid pathway for drug administration, but are self-sealing when removed (Note: closed connector devices do not prevent backflow and a clamp is still required on the Hickman line before removing the infusion line).

1. Sitges-Serra et al. *JPEN J Parenter Enteral Nutr.* 1984;8:668-672
2. Sitges-Serra et al. *Surgery.* 1985;97:355-357
3. Doran et al. *Adv Pulm Hypertens.* 2008;7:245-248

Split septum closed connector systems reduce the risk of bloodstream infection

- Akagi *et al* demonstrated the efficiency of closed connector systems[1]
- 20 PAH patients (24 cases) evaluated:
  - Closed connector (n=13)
  - Non-closed connector (n=11)
- CRBIs:
  - Connector closed: 0.10 per 1000 catheter days
  - Connector not closed: 0.89 per 1000 catheter days

BSI, bloodstream infection; IV, intravenous; PAH, pulmonary arterial hypertension

1. Akagi et al. *Circ J.* 2007;71:559-564

Summary of Product Characteristics for Remodulin (SmPC)

SmPC treprostinil IV

- The SmPC states that "Due to the risks associated with the permanence of central venous catheters":
  - subcutaneous infusion (of the undiluted drug) is the preferred method of administration
  - While continuous intravenous infusion should be reserved for patients *stabilised with subcutaneous treprostinil infusion*
  - *...who have* developed intolerance to the subcutaneous route
  - ... for whom such risks are considered acceptable."

- The medical team responsible for the treatment must ensure that the patient is properly instructed and competent in the use of the chosen infusion device

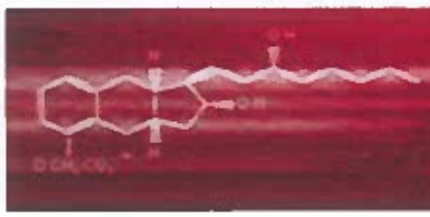
SmPC treprostinil IV

- To reduce the risk of catheter-related bloodstream infections, it is recommended to:
  - follow general principles in line with current best practice guidelines;
  - use a 0.2 micron in-line filter situated between the infusion tubing and the catheter connector;
  - use a split septum closed connector system to ensure that the catheter lumen is sealed each time the infusion system is switched off;
  - additionally ensure that the luer lock interconnections are kept dry when changing either the infusion line or the closed connector;
  - the diluted treprostinil solution should only be used for a maximum of 24 hours.

Identification and reporting of suspected CRBIs, dosage errors and pump/infusion line malfunctions

Patient questionnaire

- In order for UTEL to analyse the impact and acceptability of risk reduction actions for patients, a questionnaire will be presented to each patient receiving IV treprostinil treatment by their Healthcare Professional (HP).
  - The questionnaire will be given by an HP for completion 3 to 6 months after the start of treatment
  - In addition, the questionnaire should be completed in conjunction with the "Event of Special Interest" form, which is used to report all suspected bloodstream infections
- The questionnaire:
  - gives patients time to think about their answers carefully, without interference from, for example, an interviewer;
  - provides standardisation as each patient will receive an identical set of questions; As the questions are mainly closed-ended, the answers will be standardised, which will help in interpreting the data.
  - addresses a number of pertinent issues and questions relatively effectively, with the likelihood of a high response rate.
  - Completed questionnaires are collected by the local Business Partner and returned to UTEL by the HCP within an appropriate timeframe. The data are analysed and reported by UTEL's Medical Affairs Department and UT's Pharmacovigilance Department.



Administration by continuous intravenous infusion

- Treprostinil IV is administered by continuous infusion via a central venous catheter using an ambulatory infusion pump.
  - It can also be administered temporarily via a peripheral venous cannula, preferably placed in a large vein.
  - The use of peripheral infusion for more than a few hours may be associated with an increased risk of thrombophlebitis
- Pumps for subcutaneous infusion should be avoided in favour of dedicated IV pumps
  - Subcutaneous pumps generally run at 0.1-0.2 ml/h and administer the undiluted medication taken directly from the vial into the syringe reservoir
  - Higher concentrations of the medication increase the risk of overdose if an accidental bolus is given
  - These pumps work at relatively low infusion rates, which increases the risk of catheter occlusion

Administration by continuous intravenous infusion

- To avoid any interruptions in the administration of the drug, the patient should have access to an infusion pump and spare infusion sets in case the administration equipment ceases to work properly.
- In the event of problems, patients should be taught to:
  - check the infusion pump and connections at the first sign of unexplained breathlessness or any other deterioration in their state of health;
  - recognise the signs of overdose (hot flushes, headache, jaw pain, nausea, diarrhoea, weakness);
  - seek urgent help, which may result in the temporary suspension of the infusion system until it can be checked.
- Any suspected medication errors, overdose, catheter occlusion, etc. should be carefully monitored and reported using the standard post-marketing safety report available from United Therapeutics or the local Remodulin distributor.

Choosing a suitable infusion pump

- A pump specifically designed for continuous IV administration should be chosen. In general, the ambulatory infusion pump should be:
  - small and light;
  - able to adjust the infusion rate by increments of approximately 0.05 ml/h: typical infusion rates should be between 0.4 ml/h and 2 ml/h;
  - equipped with alarms against obstruction/non-administration, low battery, programming errors and motor malfunctions;
  - have an accuracy equal to or greater than +/- 6% of the hourly administration rate;
  - have a reservoir made of polyvinyl chloride, polypropylene or glass.

Calculation of solutions IV

- Example studied: for a 70 kg person taking a dose of 30 ng/kg/min and using a 20 ml syringe, a 2 ml tube of preparation volume and with the 2.5 mg/ml vial
- First calculate the concentration needed in the syringe:

  (dose) 30 ng/kg/min x *(weight)* 70 kg x 0.00006* = 0.15 mg/ml

  (infusion rate) 0.83 ml/h if using pump 20 ml/day

- Next, calculate the volume of medication to be removed from the bottle:

  (diluted concentration) 0.15 mg/ml X *(reservoir + preparation volume)* 22 ml = 1.3 ml

  (dosage) 2.5 mg/ml

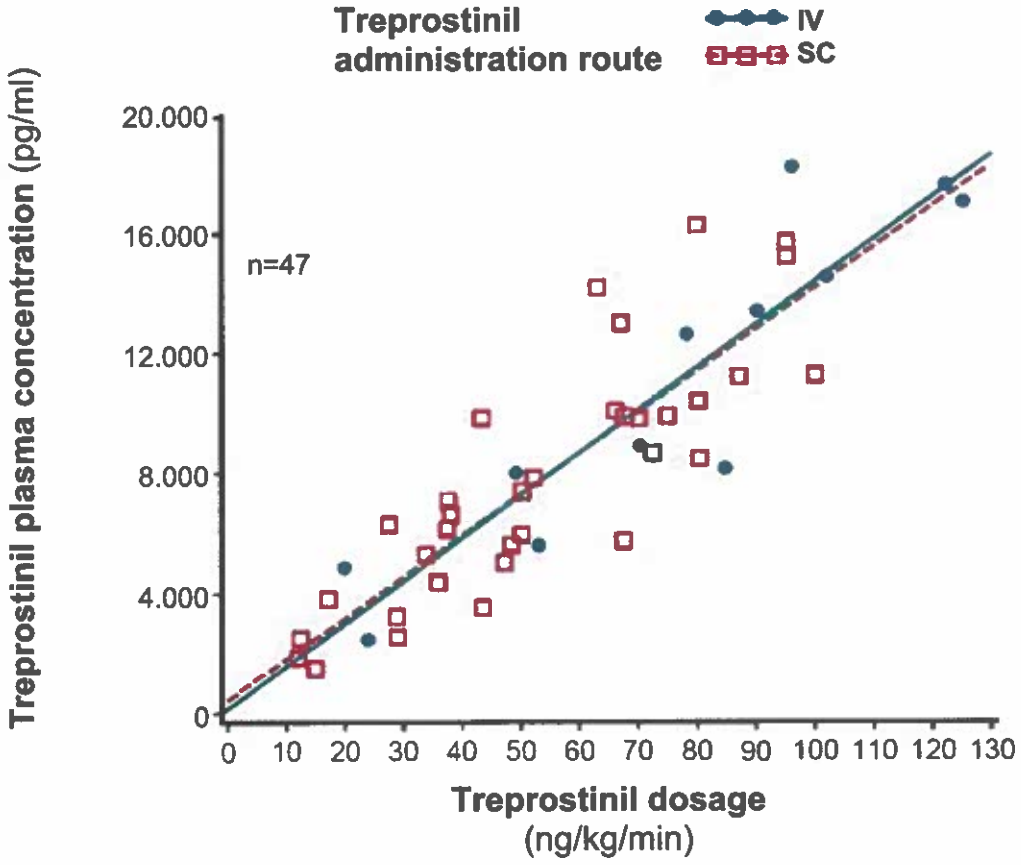
- Then add saline solution to reach the total (1.3 ml treprostinil + 20.7 ml saline solution) = 22 ml

* The multiplier 0.00006 converts from ng/min to mg/h

Transition from SC to IV treprostinil

Bioequivalence of treprostinil SC/IV

- In PAH patients, increasing the dose of SC or IV treprostinil increases plasma concentrations linearly.
- **Conclusion:** Plasma concentrations of treprostinil have a predictable relation to the dose of treprostinil



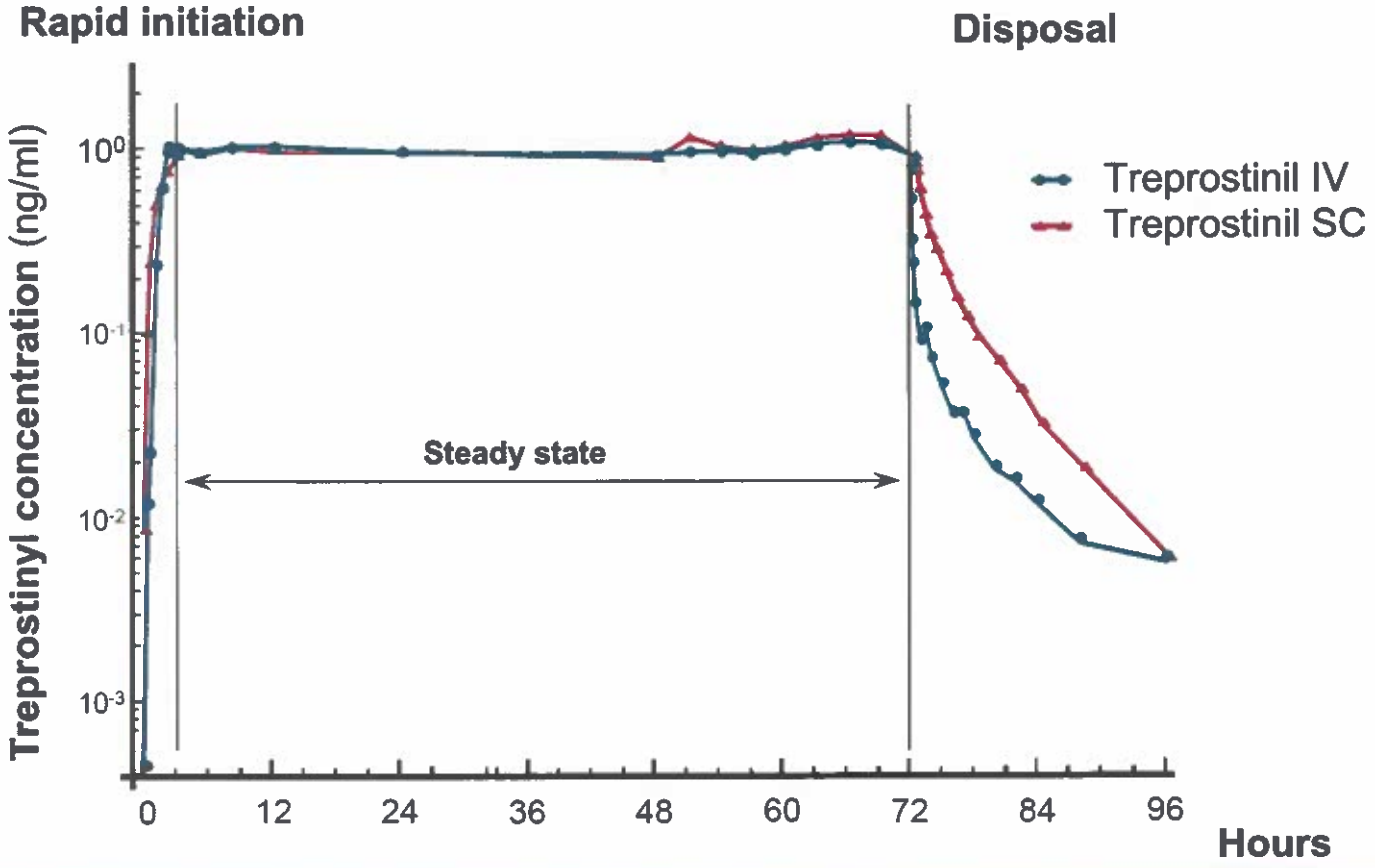
IV, intravenous; PAH, pulmonary arterial hypertension; PK, pharmacokinetics; SC, subcutaneous

McSwain et al. *J Clin Pharmacol.* 2008;48:19-25

Remodulin (treprostinil) infusion solution SmPC 23 December 2011

Bioequivalence of treprostinil SC/IV

- Plasma concentrations of treprostinil within 72 hours of SC or IV administration [1]



IV, intravenous; SC, subcutaneous

Laliberte et al. *J Cardiovasc Pharmacol.* 2004;44:209-214

Transition from SC to IV treprostinil

- When planning to switch from SC to IV infusion:
  - Choose an ambulatory pump capable of faster flow rates than the SC microinfusion pumps used for undiluted drugs
  - Be careful when recalculating the concentration and infusion rates required for the diluted administration system
  - Make sure the patient has been properly instructed, knows how to handle the new pump and connection lines and is aware of the risk management strategies to prevent CRBIs.
  - Always make the transition under medical supervision
  - Watch out for signs of transient overdose (headaches, hot flushes, etc.) and be prepared to stop the IV infusion for a short time if necessary, as there may be a short deposit effect at the previous SC administration site, with residual drug release

IV, intravenous; SC, subcutaneous

CRBI summary

- CRBIs are potentially serious complications in patients who require IV infusion treatment administered via a CVC.
- Compared to other chronic diseases, the incidence of CRBIs is very low in PAH[1-5] but proper patient education and constant monitoring are essential.
- The available data suggests that the incidence of CRBIs due to gram-negative organisms is slightly higher with IV treprostinil compared to IV epoprostenol, despite there being significant overlap.[5]
- CRBI rates can be further reduced by:
  - closed connection CVC systems;[4]
  - preventing water contamination;[6]
  - careful patient education and preparation, followed by continuous compliance with standards of good hygiene and the vigilance of healthcare providers and patients.

BSI, bloodstream infection; BSI-CSIs, catheter-related bloodstream infections; CVC, central venous catheter; IV, intravenous; PAH, pulmonary arterial hypertension

1. van Hoff et al. *J Clin Oncol.* 1990;8:1255-1262; 2. Decker et al. *Pediatr Clin North Am.* 1988;35:579-612; 3. Moureau et al. *J Vasc Interv Radiol.* 2002;13:1009-1101; 4. Akagi et al. *Circ J.* 2007;71:559-564; 5. Barst et al. *MMWR Morb Mortal Wkly Rep.* 2007;56:170-172; 6. Doran et al. *Adv Pulm Hypertens.* 2008;7:245-248

Summary of essential patient instruction

- Summary of essential patient instruction
  - Hand hygiene.
  - Preparing the area.
  - Maintenance and observation of the catheter insertion site and its protection
  - The importance of using line filters and closed connection systems.
  - It is important to keep the connection devices dry and to use waterproof covers or protections when showering or bathing.
  - It is important to avoid swimming or any other direct risk of contact between the connections or linings of the perfusions and water.
  - Pay attention to the signs of suspected CRBIs and adverse events, as well as the importance of reporting them in good time to the healthcare professional.

Summary of this session

- CRBI risk history
  - Retrospective study by the Centres for Disease Control on CRBIs
  - Background to the incidence of bloodstream infections
  - Pulmonary Hypertension Association catheter care guidelines
- Practical techniques for reducing CRBIs
  - Patient instruction and essential general principles
  - 0.2 micron line filter
  - Closed split septum connector and waterproof coating
- Remodulin (treprostinil) infusion solution SmPC
- Patient questionnaire
- Identification and reporting of suspected CRBIs, dosage errors and pump/infusion line malfunctions
  - Monitoring risk minimisation
  - Administration by continuous intravenous infusion
  - Infusion pumps suitable for IV administration: Volumetric and syringe devices
  - Calculation of the required infusion rate and concentration
- Transition from SC to IV treprostinil
  - Bioequivalence between SC and IV
- Abstract:
  - CRBI summary
  - Summary of essential patient instruction
- Suggested bibliography

Suggested bibliography

Doran A. K, Ivy D. D, Barst R.J, et al "Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension" International Journal of Clinical Practice. 2008 62(s160): 5-9

Akagi S, Matsubara H, Ogawa A, et al "Prevention of catheter-related infections using a closed hub system in patients with pulmonary arterial hypertension" Circ J. 2007 71(4):559-64

Ivy DD, Calderbank M, Wagner BD, et al "Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension" Infect Control Hosp Epidemiol. 2009 30(9):823-9

ADR Reporting

Suspected Adverse Drug Reactions or medication errors should be reported to the Malta Medicines Authority via the ADR reporting form, available online at http://www.medicinesauthority.gov.mt/adrportal.

The ADR reporting form can be sent by post to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or via email to postlicensing.medicinesauthority@gov.mt.

Alternatively, adverse drug reactions can also be reported to Central Procurement & Supplies Unit, (Head Office),UB002, Industrial Estate, San Gwann - SGN3000 or via email: info.cpsu@gov.mt.