SANDOZ
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Prescriber Guide

Information for healthcare professionals involved in the prescribing or dispensing of Rivaroxaban

This educational material is part of the marketing authorisation and has been approved by the HPRA

Contents

RIVAROXABAN ROWEX 10 MG, 15 MG & 20 MG FILM-COATED TABLETS
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1. Patient Alert Card

A patient alert card must be provided to each patient who is prescribed rivaroxaban 10, 15 or 20 mg, and the implications of anticoagulant treatment should be explained. Specifically, the need for compliance, the need to take the 15 mg and 20 mg strengths with food, signs of bleeding, and when to seek medical attention should be discussed with the patient or caregiver.

The patient alert card will inform physicians and dentists about the patient's anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every health care provider, especially if they need to have surgery or other invasive procedures.

2. PRESCRIBER GUIDE

The Prescriber Guide provides recommendations for the use of rivaroxaban in order to minimise the risk of bleeding during treatment with rivaroxaban.

For further information and additional details on Rivaroxaban, please see the Summary of Product Characteristics (SmPC).
The Prescriber Guide does not substitute the Rivaroxaban SmPC. Before prescribing please also read the Rivaroxaban SmPC.

3. Dosing Recommendations

a) Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
The recommended dose for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA) is 20 mg once daily with food

i) Duration of therapy:
Rivaroxaban should be continued long term provided the benefit of stroke and systemic embolism prevention therapy outweighs the potential risk of bleeding.

ii) Missed dose:
If a dose is missed the patient should take rivaroxaban immediately and then continue the following day with once daily intake as before.

iii) Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement
There is limited experience of a reduced dose of 15 mg rivaroxaban once daily (or 10 mg rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement.

iv) Patients undergoing cardioversion
Rivaroxaban can be initiated or continued in patients who may require cardioversion.

For transoesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken rivaroxaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

v) Patients with renal impairment
Patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29 ml/min) renal impairment treated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation should be treated with 15 mg once daily.

Patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29 ml/min) renal impairment treated for acute DVT, acute PE and prevention of recurrent DVT and PE should be treated with rivaroxaban 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily.

A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic (PK) modelling and has not been studied in this clinical setting.

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 mL/min). The use of rivaroxaban is not recommended in patients with creatinine clearance < 15 mL/min.

When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

b) Dosing in treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults and treatment of venous thromboembolism (VTE) and prevention of recurrence in children and adolescents
i) Adults
Adult patients are initially treated with 15 mg **twice daily** for the first 3 weeks for the initial treatment of DVT or PE This initial treatment is followed by 20 mg **once daily** for the continued treatment period.

ii) Duration of therapy (adults)
Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE
When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months' therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated co-morbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.
The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding

Rivaroxaban 10 mg is not recommended for the initial 6 months' treatment of DVT or PE.

	Time period	Dosing schedule	Total daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

iii) Missed dose (adults)

- twice daily treatment period (15 mg bid for the first three weeks):
  If a dose is missed, the patient should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
- once daily treatment period (beyond three weeks):
  If a dose is missed, the patient should take rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

iv) Patients with renal impairment (adults)

Patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29 ml/min) renal impairment treated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation should be treated with 15 mg once daily.

Patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29 ml/min) renal impairment treated for acute DVT, acute PE and prevention of recurrent DVT and PE should be treated with Rivaroxaban 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily.
A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic (PK) modelling and has not been studied in this clinical setting.

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 mL/min). The use of Rivaroxaban is not recommended in patients with creatinine clearance < 15 mL/min.

When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

v) Children

Rivaroxaban treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1). The dose for children and adolescent is calculated based on body weight.

- Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.

- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of Rivaroxaban granules for oral suspension.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

vi) Duration of treatment (children)

Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

vii) Missed dose (children)

A missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

On the following day, the child should continue with the regular daily regimen.

viii) Patients with renal impairment (children)

Children with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m2) no dose adjustment is required, based on data in adults and limited data in paediatric patients.

Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2) Rivaroxaban is not recommended as no clinical data is available.

c) Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.

i) Duration of treatment

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

ii) Missed dose

If a dose is missed the patient should take rivaroxaban immediately and then continue the following day with once daily intake as before.

iii) Patients with renal impairment

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min.

- For the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30- 49 ml/min).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, no dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's
assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting.
When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

4. Oral Intake
Rivaroxaban 10 mg:
Rivaroxaban 10 mg can be taken with or without food.
For patients who are unable to swallow whole tablets, rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.
The crushed rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water.

Rivaroxaban 15 mg and 20 mg:
Rivaroxaban 15 mg and 20 mg must be taken with food.
The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability.

For patients who are unable to swallow whole tablets, rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

Children
For children weighing ≥30 kg if the oral suspension is not immediately available, when doses of Rivaroxaban 15 mg or 20 mg are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administered orally.
The crushed Rivaroxaban tablet may be given through nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Rivaroxaban. Avoid administration of Rivaroxaban distal to the stomach.

5. Perioperative Management
If an invasive procedure or surgical intervention is required, rivaroxaban 10 mg, 15 mg and 20 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Rivaroxaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

6. Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

There is no clinical experience with the use of 15/20 mg rivaroxaban tablets in adults, nor with the use of Rivaroxaban in children in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the removal of an epidural catheter and based on the general pharmacokinetic (PK) characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2 of the SmPC).

Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered. If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

No data is available on the timing of the placement or removal of neuraxial catheter in children while on Rivaroxaban. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

7. Converting from Vitamin K Antagonists (VKA) to Rivaroxaban

For adults and paediatrics treated for prevention of stroke and systemic embolism, treatment with Vitamin K Antagonists (VKA) should be stopped and rivaroxaban therapy should be initiated when the INR is ≤ 3.0.

For patients treated for DVT, PE and prevention of recurrent DVT and PE, treatment with VKA should be stopped and rivaroxaban therapy be initiated when the INR is ≤ 2.5.

INR measurement is not appropriate to measure the anticoagulant activity of rivaroxaban, and therefore, should not be used for this purpose. Treatment with rivaroxaban only does not require routine coagulation monitoring.

8. Converting from Rivaroxaban to Vitamin K Antagonists (VKA)

It is important to ensure adequate anticoagulation while minimizing the risk of bleeding during conversion of therapy.

a) Adults

When converting from rivaroxaban to VKA, rivaroxaban and VKA should be given overlapping until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activity of rivaroxaban. While patients are on both rivaroxaban and VKA the **INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban**. Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose reliably reflect the VKA dosing.

b) Children

Children who convert from Rivaroxaban to VKA need to continue Rivaroxaban for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Rivaroxaban. Co-administration of Rivaroxaban and VKA is advised to continue until the INR is ≥ 2.0. Once Rivaroxaban is discontinued, INR values obtained at least 24 hours after the last dose reliably reflect the VKA dosing.

9. Converting from Parenteral Anticoagulants to Rivaroxaban

- For adults and paediatrics patients with continuously administered parenteral medicinal product such as intravenous unfractionated heparin:
  Start rivaroxaban at the time of discontinuation.
- Patients with parenteral medicinal product on a fixed dosing scheme such as
  LMWH:
  Discontinue parenteral medicinal product and start rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product.

10. Converting from Rivaroxaban to Parenteral Anticoagulants

The first dose of parenteral anticoagulant should be given at the time that the next rivaroxaban dose would have been due.

11. Populations Potentially at Higher Risk of Bleeding

Like all anticoagulants, Rivaroxaban may increase the risk of bleeding.
Therefore, Rivaroxaban is contraindicated in patients

- with active clinically significant bleeding
- with a lesion or condition at significant risk for major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients
- receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

a) Elderly population:

The risk of bleeding increases with increasing age.
Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications.

Treatment decision in these patients should be carried out after assessment of treatment benefit against the risk for bleeding.

b) Patients with renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk.

Rivaroxaban is to be used with caution in patients with creatinine clearance 15 – 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations. Rivaroxaban is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data is available.

c) Patients concomitantly receiving other medicinal products:

- Systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): use of rivaroxaban is not recommended
- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). After an acute coronary syndrome, patients on treatment with Rivaroxaban and ASA or Rivaroxaban and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients (for patients with renal impairment see further above).

d) Patients with other haemorrhagic risk factors

As with other antithrombotics, Rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, esophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

e) Patients with cancer

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during Rivaroxaban therapy.

In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban is contraindicated.

12. Other contraindications

Rivaroxaban is contraindicated during pregnancy and breast-feeding. Women of childbearing potential should avoid becoming pregnant during treatment with Rivaroxaban.

Rivaroxaban is also contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

13. Overdose

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg Rivaroxaban and above; however, no data is available at supratherapeutic doses in children. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found in children, suggesting absorption limitations for higher doses, even when taken together with food. A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa).
The use of activated charcoal to reduce absorption in case of overdose may be considered.

Should a bleeding complication arise in a patient receiving Rivaroxaban, the next Rivaroxaban administration should be delayed, or treatment should be discontinued as appropriate.
Individualized bleeding management may include

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa) or a of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban.

Due to the high plasma protein binding rivaroxaban is not expected to be dialyzable.

14. Coagulation Testing

Rivaroxaban does not require routine coagulation monitoring. However, measuring rivaroxaban levels may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to take clinical decisions, e.g. overdose and emergency surgery.

Anti-FXa assays with rivaroxaban-specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated, haemostatic status can also be assessed by Prothrombin time using Neoplastin as described in the SmPC.

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalized ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure the activity of rivaroxaban. Dosing or treatment decisions should not be based on results of INR except when converting from rivaroxaban to VKA as described above.

15. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance; website: www.hpra.ie