Prescriber Guide
For
Xanirva film-coated tablets

This guide is to be used to support the appropriate use of Xanirva in the following indications:

- Prevention of stroke and systemic embolism in eligible adults with non-valvular atrial fibrillation (AF)
- Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults and children (not recommended for use in haemodynamically unstable PE patients)
- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events, in combination with acetylsalicylic acid (ASA)
- Prevention of atherothrombotic events in adults after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, in combination with anti-platelet therapy

It includes the following information:

- **• Dosing recommendations**
- **• Oral intake**
- **• Perioperative management**
- **• Contraindications**
- **• Overdose**
- **• How to manage bleeding complications**
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Prescriber Guide

The Prescriber Guide provides recommendations for the use of Xanirva in order to minimise the risk of bleeding during treatment with Xanirva. The Prescriber Guide does not substitute the] Summary of Product Characteristics (SmPC).

Patient alert card

A patient alert card is provided with the product package to each patient who is prescribed Xanirva 2.5mg, 10mg, 15mg or 20mg tablets or capsules.

Please explain the implications of anticoagulant treatment to patients and/or caregiver, in particular highlighting the need for:

- Treatment compliance
- Taking medication with food (for 15mg and 20mg only)
- Recognising signs or symptoms of bleeding
- When to seek medical attention

The patient alert card will inform treating physicians and dentists about the patient‘s anticoagulation treatment and will contain emergency contact information.

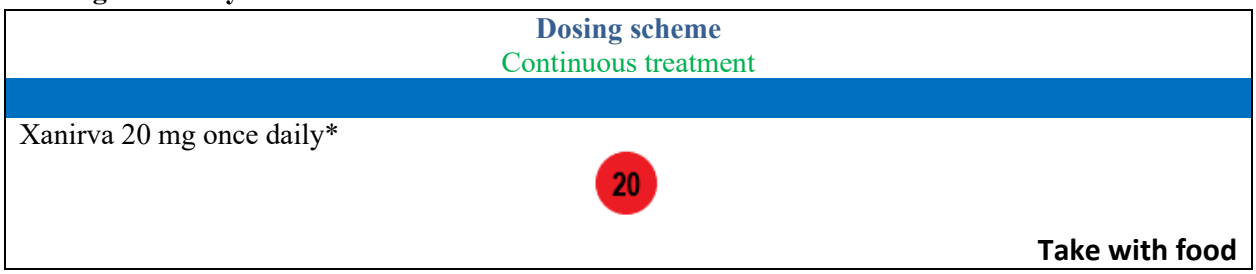
Please instruct patients or caregiver to carry the patient alert card with them at all times and present it to every healthcare provider. Please also instruct the patient to tick the appropriate box on the patient alert card corresponding to the dose that they are taking.

1. Dosing recommendation

Adult: Stroke prevention in adult patients with non-valvular AF

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.

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular AF is **20 mg once daily**.



In patients with **moderate or severe renal impairment the recommended dose is **15 mg once daily**.*

Patients with renal impairment:

In patients with moderate (creatinine clearance 30-49 ml/min) or severe (15-29 ml/min) renal impairment the recommended dose is 15 mg once daily. Xanirva is to be used with caution in patients with severe renal impairment as limited clinical data indicates a significantly increased plasma concentration. Use is not recommended in patients with creatinine clearance < 15 ml/min.

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

Duration of therapy:

Xanirva should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding.

Missed dose:

If a dose is missed the patient should take Xanirva 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.

Patients with non-valvular atrial fibrillation undergoing PCI (percutaneous coronary intervention) with stent placement:

There is limited experience of a reduced dose of 15 mg Xanirva once daily (or 10 mg Xanirva once daily for patients with moderate renal impairment [creatinine clearance 30-49 ml/min]) in addition to a $P2Y_{12}$ inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement.

Patients undergoing cardioversion:

Xanirva can be initiated or continued in patients who may require cardioversion.

For transoesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Xanirva 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

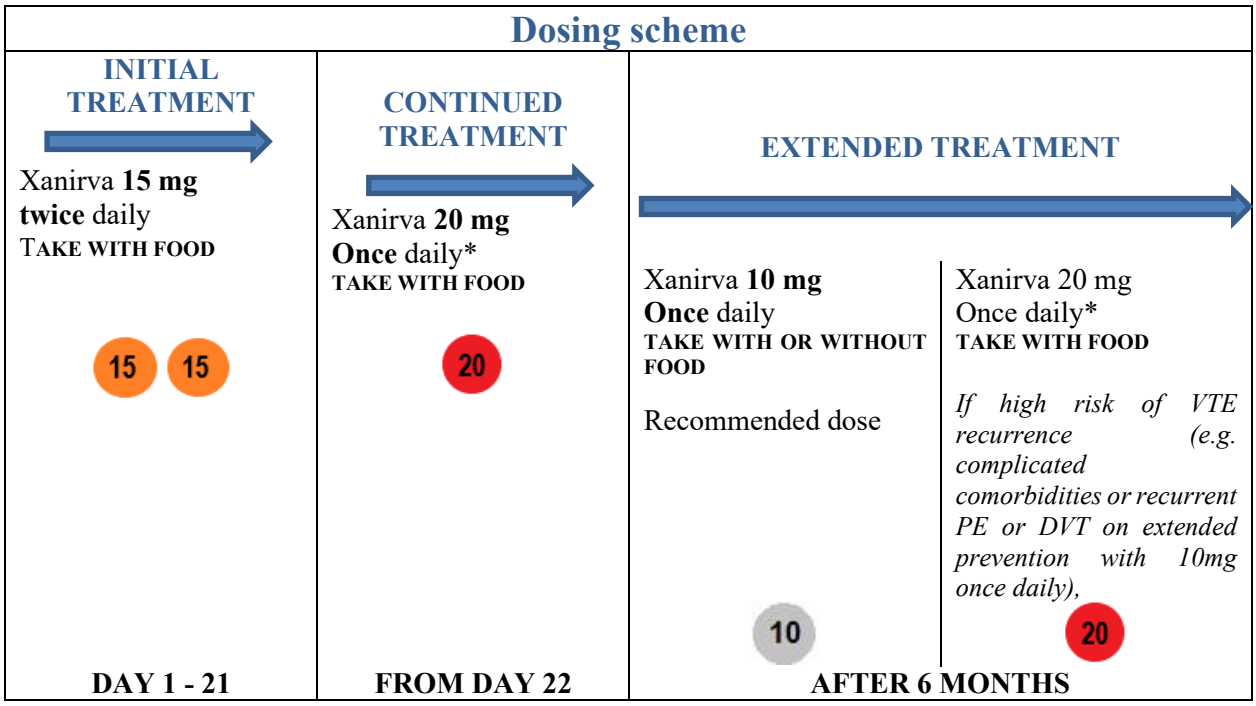
taken Xanirva as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients and in children

Adults

Adult patients are initially treated with 15mg **twice daily** for the first three weeks. This initial treatment is followed by 20 mg **once daily** for the continued treatment period. 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 comorbidities, or who have developed **recurrent DVT or PE on extended prevention** with Xanirva 10mg once daily, a dose of Xanirva **20 mg once daily** should be **considered**.

Xanirva 10mg is **NOT** recommended for the initial 6 months treatment of DVT or PE.



**Patients with DVT/PE and renal impairment may be considered for dose reduction.*

Children

Xanirva 15 mg Tablets/Capsules, Xanirva 20 mg Tablets/Capsules can be used to achieve the appropriate weight-based dose.

- For children and adolescents weighing ≥30 and <50kg, use the **15 mg** tablet or capsule **once daily**.
- For children and adolescents weighing ≥50kg, use the **20 mg** tablet or capsule **once daily**.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of rivaroxaban containing products in the form of granules for oral suspension.

Treatment (using the most appropriate formulation) of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg (15 mg strength) or more than 50 kg (20 mg strength) after at least 5 days of initial parenteral anticoagulation treatment.

Patients with renal impairment:

Adults

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 Xanirva 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. Xanirva is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min. When the recommended dose is 10 mg once daily (after ≥6 months of therapy), no dose adjustment from the recommended dose is necessary.

Xanirva should be used with caution in patients with renal impairment concomitantly (with moderate renal impairment – CrCl 30-49 ml/min for Xanirva 10 mg) receiving other medicinal products which increase rivaroxaban plasma concentrations.

Children

No dose adjustment is required for children and adolescents with mild renal impairment (glomerular filtration rate: 50 ml ≤ 80 ml/min/1.73 m2), based on data in adults and limited data in paediatric patients.

Xanirva is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate <50 ml/min/1.73 m2), as no clinical data is available.

Duration of therapy:

Adults

Short duration of therapy Xanirva should be considered in patients with DVT/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/PE not related to major transient risk factors, unprovoked DVT/PE, or a history of recurrent DVT/PE.

Children

All children, except those aged <2 years with catheter-related thrombosis

Therapy with Xanirva should be continued for at least 3 months. Treatment can be extended up to 12 months when clinically necessary. 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.

Missed dose:

Adults

Twice-daily treatment period (15 mg twice daily for the first 3 weeks)

If a dose is missed, the patient should take Xanirva immediately to ensure intake of 30 mg Xanirva per day. In this case, two 15 mg tablets may be taken at once. Continue with the regular 15 mg twice-daily intake on the following day.

Once-daily treatment period (beyond 3 weeks)

If a dose is missed, the patient should take Xanirva 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.

Children

Once daily regimen

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.

Two times daily regimen

A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening.

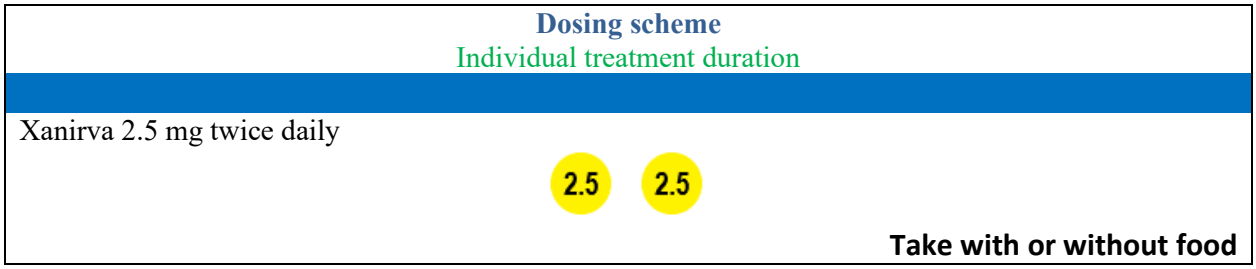
• *Three times daily regimen*

The three times daily administration schedule with approximately 8-hour intervals should be resumed at the next scheduled dose without compensating for the missed dose.

On the following day,

the child should continue with the regular once, twice, or three times daily regimen.

Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.



Patients taking Xanirva 2.5 mg twice daily should also take a daily dose of 75–100 mg acetylsalicylic acid (ASA).
In patients after a successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD, treatment should not be started until haemostasis is achieved.

Patients with renal impairment:
No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30-49ml/min). Xanirva is to be used with caution in patients with severe renal impairment (CrCl 15-29 ml/min) and is not recommended in patients with CrCl <15 ml/min.
In patients with moderate renal impairment (CrCl 30-49 ml/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations, Xanirva is to be used with caution.

Duration of therapy:
Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

Co-administration with antiplatelet therapy
In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Xanirva 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.

Other warnings and precautions in CAD/PAD patients
In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of Xanirva 2.5 mg twice daily have been investigated in combination with ASA.

In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of Xanirva 2.5 mg twice daily have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel. If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided. Patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due

to symptomatic PAD were allowed to additionally receive standard dose of clopidogrel once daily for up to 6 months (see also section 5.1 of the SmPC).

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

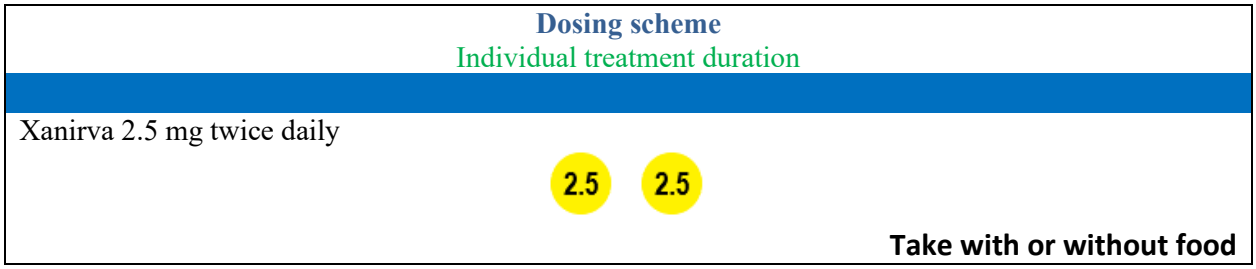
Concomitant treatment of CAD/PAD with Xanirva 2.5 mg twice daily and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. Treatment with Xanirva 2.5 mg should be avoided in patients with previous stroke or TIA receiving dual antiplatelet therapy.

Xanirva co-administered with ASA should be used with caution in CAD/PAD patients:
• ≥75 years of age. The benefit-risk of the treatment should be individually assessed on a regular basis
• With a lower weight (<60 kg)
• In CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with Xanirva. (See section 5.1 of the SmPC for further clarification.)

Missed dose:

If a dose is missed, the patient should continue with the regular 2.5 mg Xanirva dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers



In addition to Xanirva 2.5 mg, patients should also take a daily dose of 75-100 mg ASA or a daily dose of 75-100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.

The recommended dose of Xanirva is 2.5 mg **twice daily**, starting as soon as possible after stabilisation of the index ACS event but at the earliest 24 hours after hospital admission and at the time when parenteral anticoagulation therapy would normally be discontinued.

Patients with renal impairment:

No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30-49 ml/min). Xanirva is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 ml/min) and is not recommended in patients with creatinine clearance <15 ml/min.

In patients with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Xanirva is to be used with caution.

Duration of therapy:

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited.

Co-administration with antiplatelet therapy

In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Xanirva 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.

Other warnings and precautions in ACS patients

In recent ACS patients, efficacy and safety of Xanirva 2.5 mg twice daily have been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ticlopidine.
Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

Xanirva co-administered with ASA or with ASA plus clopidogrel or ticlopidine should be used with caution in ACS patients:
• ≥75 years of age. The benefit-risk of the treatment should be individually assessed on a regular basis
• With a lower weight (<60 kg)

Concomitant treatment of ACS with Xanirva and antiplatelet therapy is contraindicated in patients with a prior stroke or a transient ischaemic attack (TIA).

Missed dose:

If a dose is missed, the patient should continue with the regular 2.5 mg Xanirva dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

Adult: Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

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

Dosing scheme Individual treatment duration
Xanirva 10 mg once daily  **Take with or without food**

Duration of therapy:

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.

Missed dose:

If a dose is missed the patient should take Xanirva immediately and then continue the following day with once daily intake as before. The dose should not be doubled within the same day to make up for a missed dose.

2. Oral intake

Xanirva 2.5 mg and 10 mg tablets or capsules can be taken with or without food.
Xanirva 15 mg and 20 mg tablets or capsules are to 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.

Adults

For patients who are unable to swallow whole tablets/capsules:

- **tablet** may be **crushed** and **mixed** with water or apple puree immediately prior to use and then administered orally. After the administration of crushed Xanirva 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed Xanirva tablet or sprinkled capsule may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet/ sprinkled capsule 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/sprinkled Xanirva 15 mg or 20 mg film-coated tablets/capsules, the dose should then be immediately followed by enteral feeding.

Children

For children weighing ≥30 kg who are unable to swallow whole tablets/capsules, Other rivaroxaban-containing products granules for oral suspension should be used. 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 or springling capsules and mixing it with water or apple purée immediately prior to use and administered orally.

The oral suspension and the crushed Xanirva tablet/sprinkled capsule may be given through nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Xanirva. Avoid administration of Xanirva distal to the stomach.

3. Perioperative management

If an invasive procedure or surgical intervention is required, if possible and based on the clinical judgement of the physician:

- Xanirva 10/15/20 mg should be stopped at least 24 hours before the intervention
- Xanirva 2.5 mg should be stopped at least 12 hours before the intervention

If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention.

Xanirva 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.

4. 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 post-operative 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.

Indication-specific recommendations

Prevention of stroke and systemic embolism in adult patients with NVAF/ Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients/ Treatment of VTE and prevention of VTE recurrence in children

There is no clinical experience with the use of 15 mg and 20 mg Xanirva tablets/capsules in adults nor with the use of Xanirva in children in these situations. To reduce the potential risk of bleeding associated with the concurrent use of Xanirva and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Xanirva. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Xanirva is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.
For the removal of an epidural catheter and based on the general pharmacokinetic characteristics, at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients, should elapse after the last administration of Xanirva (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Xanirva dose is administered. If traumatic puncture occurs, the administration of Xanirva is to be delayed for 24 hours.
No data is available on the timing of the placement or removal of a neuraxial catheter in children while on Xanirva. Discontinue Xanirva and consider a short-acting parenteral anticoagulant.

Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

To reduce the potential risk of bleeding associated with the concurrent use of Xanirva and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Xanirva.
Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Xanirva is estimated to be low (see section 5.2 of the SmPC).
At least 18 hours should elapse after the last administration of Xanirva before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next Xanirva dose is administered. If traumatic puncture occurs, the administration of Xanirva is to be delayed for 24 hours.

Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events/

Prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers

There is no clinical experience with the use of Xanirva 2.5 mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

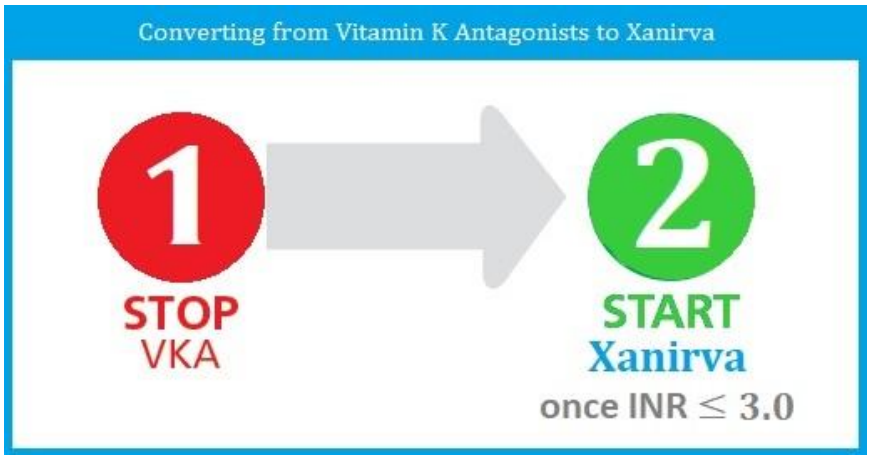
To reduce the potential risk of bleeding associated with the concurrent use of Xanirva and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Xanirva.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Xanirva is estimated to be low (see section 5.2 of the SmPC). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

5. Converting from vitamin K antagonists (VKA) to Xanirva

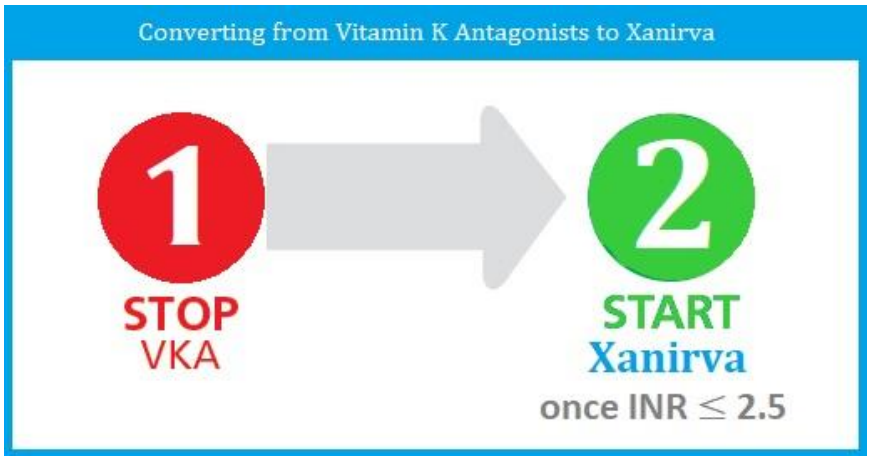
- **Prevention of stroke and systemic embolism**

For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and Xanirva therapy should be initiated when the **INR ≤3.0**.



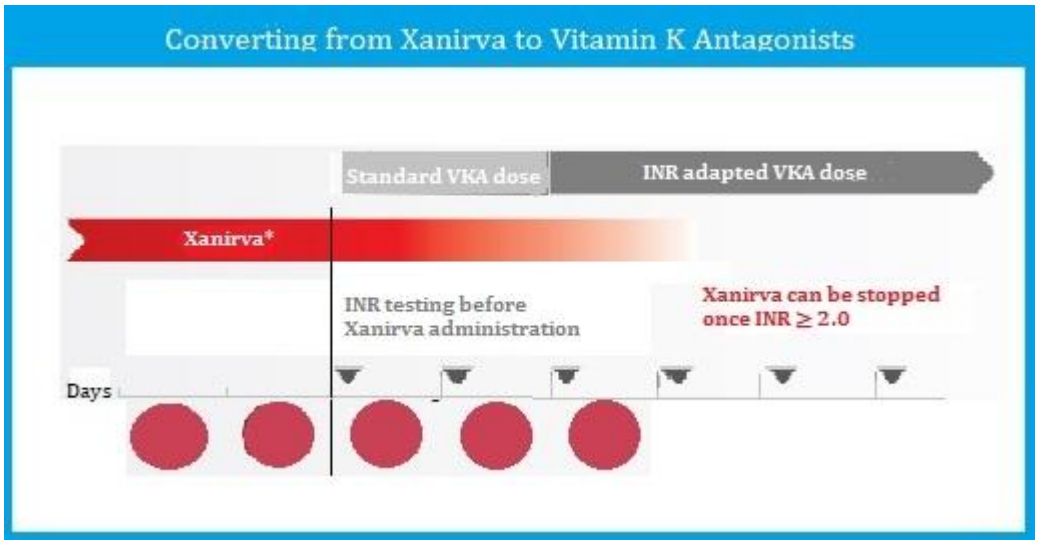
- **DVT, PE and prevention of recurrent DVT and PE**

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



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

6. Converting from Xanirva to VKA



*See dosing recommendation for required daily dose

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

Adults and children

When converting to VKA, Xanirva and VKA should be given concurrently 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 guided by INR testing.

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

Children

Children who convert from Xanirva to VKA need to continue Xanirva 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 Xanirva. Co-administration of Xanirva and VKA is advised to continue until the INR is ≥2.0.

7. Converting from parenteral anticoagulants to Xanirva

- Patients with a continuously administered parenteral drug such as intravenous unfractionated heparin: Xanirva should be started at the time of discontinuation.
- Patients with a parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start Xanirva 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

8. Converting from Xanirva to parenteral anticoagulants

Give the first dose of the parenteral anticoagulant at the time the next Xanirva dose would have been taken.

9. Populations potentially at higher risk of bleeding

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

- With clinically significant active bleeding.
- With a lesion or condition, if considered to be a significant risk of major bleeding. This may include 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.
- Receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from Xanirva or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- With hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients.

Elderly population: the risk of bleeding increases with increasing age.

Several subgroups of patients are at increased risk 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.

Patients with renal impairment:

For adults, see dosing recommendations for patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment. Xanirva is to be used with caution in patients with CrCl 15–29 ml/min and in patients with renal impairment concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations. Use of Xanirva is not recommended in patients with CrCl <15 ml/min.

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 Xanirva is not recommended.
- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
- ACS patients and CAD/PAD patients: Patients treated with antiplatelet agents 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).

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The warnings above should be taken into account also for the paediatric population.

Patients with other haemorrhagic risk factors:

As with other antithrombotic, Xanirva 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, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding.

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 (see further above).

10. Other contraindications

Xanirva is contraindicated during pregnancy and breastfeeding. Women of childbearing potential should avoid becoming pregnant during treatment with Xanirva. Xanirva is also contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

11. Overdose

Due to limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg Xanirva and above in adults; 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); however, it is not established in children. The use of activated charcoal to reduce absorption in case of overdose may be considered.

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

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

Due to the high plasma protein binding Xanirva is not expected to be dialysable.

12. Coagulation testing

Xanirva does not require routine coagulation monitoring. However, measuring Xanirva levels may be useful in exceptional situations where knowledge of Xanirva exposure may help to make clinical decisions, e.g. overdose and emergency surgery.
Anti-FXa assays with Xanirva-(rivaroxaban) specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated haemostatic status can also be assessed by PT 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 normalised 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 activity of Xanirva.
Dosing or treatment decisions should not be based on results of INR except when converting from Xanirva to VKA as described above.

13. Dosing overview table

Indication	Dosing	Special patient population
Stroke prevention In adult patients with non-valvular atrial fibrillation[a]	**Xanirva 20 mg once daily**	**Impaired renal function with CrCl 15-49ml/min[b]:** **Xanirva 15 mg once daily** **PCI with stent placement** (for max. 12 months): - **Xanirva 15 mg once daily** plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel) **PCI with stent placement** *in patients with impaired renal function CrCl 30 -49ml/min[b])* **- Xanirva 10 mg once daily** plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel)
Treatment of **DVT** and **PE**[c], and **prevention** of recurrent **DVT** and **PE**:	Adults: **Treatment & prevention of recurrence:** *Day 1-21*: **Xanirva 15 mg twice daily** **Prevention of recurrence**: *Day 22 onwards*: **Xanirva 20 mg once daily** **Extended prevention of recurrence:** from month 7 onwards: **Xanirva 10 mg once daily** **Extended prevention of recurrence** *in high risk patients*: **Xanirva 20 mg once daily** For extended prevention of recurrence, from month 7 onwards, in patients at high risk of recurrent DVT or PE, such as those: - With complicated comorbidities - Who have developed recurrent DVT or PE on extended prevention with Xanirva 10mg	*Impaired renal function with CrCl 15-49ml/min[b]:* **Treatment & prevention of recurrence:** *Day 1-21*: Xanirva 15mg **twice** daily Thereafter Xanirva 15 mg **once** daily instead of Xanirva 20mg once daily, if patient's assessed risk for bleeding outweighs risk for recurrence. When the recommended dose is Xarelto 10 mg once daily, no dose adjustment is necessary *Children (dosing is based on body weight)* **Xanirva 15 mg Tablets/Capsules,** **Xanirva 20 mg only** **Tablets/Capsules** can be used to achieve the appropriate weight-based dose. For children and adolescents weighing ≥30 and <50kg, use the 15mg tablet or capsule. For children and adolescents weighing ≥50kg, use the 20mg tablet.

Indication	Dosing	Special patient population
Prevention of VTE in adults undergoing elective **hip** or **knee replacement surgery**	**Xanirva 10 mg once daily** **Hip Replacement Surgery** 5 weeks treatment duration **Knee Replacement Surgery** 2 weeks treatment duration	
Prevention of atherothrombotic events in adult patients with **CAD** or **symptomatic PAD** at high risk of ischaemic events	Xanirva **2.5mg twice daily in combination with ASA** 75-100 mg/day	
Prevention of atherothrombotic events in adult patients **after an ACS** with elevated cardiac biomarkers	**Xanirva 2.5mg twice daily in combination with standard antiplatelet therapy** (ASA 75-100 mg/day alone or ASA 75- 100 mg/day plus clopidogrel 75 mg/day or a standard dose of ticlopidine)	

Xanirva **15 mg and 20 mg should be taken with food**[1]

For patients who are unable to swallow whole tablets/capsules:

- tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.
- content of capsule may be mixed with water or apple puree immediately prior to use and then administered orally.

[a] With one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

[b] Use with caution in patients with creatinine clearance 15-29ml/min and in patients with renal impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration.

[c] Not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

For further information, please see the SmPC.

14. Reporting suspected adverse reactions

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the information leaflet that comes in the pack. Suspected adverse reactions may also be reported to the Kosovo Agency for Medicinal Products and Medical Devices (KAMPM).

Electronically:
info@akkpm-rks.gov

By mail:
Kosovo Agency for Medicinal Products and Medical Devices (KAMPM)
Hospital Circle, n.n. (UCCK)
10000 Prishtina, Kosovo

By fax:
+383 38 512 243

You may also report suspected adverse reactions to the Marketing Authorisation Holder (MAH) in Kosovo.

Contact details of the local qualified person responsible for pharmacovigilance on behalf of the Marketing Authorisation Holder:

Tringa Rraci, MPharm
Local Person Responsible for Pharmacovigilance (LPPV)
MAH Zentiva Pharma GmbH
Pharmakos LLC

Tel: +383 49 621 621
E-mail: pharmacovigilance@pharmakos.biz
PV-Kosovo@zentiva.com

By reporting side effects you can help provide more information on the safety of this medicine.

Kind regards,

Signature: _____

Tringa Rraci

Sources of Global document:

- SmPC – for film-coated tablets (CZ/H/0834, approved 29-Feb-2024, CZ/H/0835, approved 12-Feb-2024) and hard capsules (CZ/H/0836-0837) approved 20-Jan-2024.
- RMP – version 2.0 for film-coated tablets (CZ/H/0834-0835, approved 28-Aug-2022) and version 1.2 for hard capsules (CZ/H/0836-0837, approved 22-Mar-2022)
- Educational material of the reference product Xanirva:
  - Prescriber guide version MT12 (date of preparation: December 2022, approved on 16.01.2023 by Malta Medicines Authority)
  - Patient alert card (Apr-2023)