BANORIV® (Rivaroxaban)

Healthcare Professional Educational Guide

SpimacoAddwaeih
www.spimaco.sa

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سبيماكو الدوائية
SPIMACO ADDWAEIH

BANORIV® (RIVAROXABAN) PRESCRIBER GUIDE

This guide is to be used to support the appropriate use of BANORIV® 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.
- Prevention of 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.

It includes the following information:

- Dosing recommendations
- Oral intake
- Perioperative management
- Contraindications
- Overdose
- How to manage bleeding complications
- Coagulation testing

Prescriber Guide

The Prescriber Guide provides recommendations for the use of BANORIV® in order to minimize the risk of bleeding during treatment with BANORIV®.

The Prescriber Guide does not substitute the BANORIV® Summary of Product Characteristics

(SPC).*

* https://sdi.sfda.gov.sa/

BANORIV® patient alert card

A patient alert card is provided with the product package to each patient who is prescribed BANORIV® 2.5mg, 10mg, 15mg or 20mg tablets. 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)
- Recognizing 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.

CONTENTS

ADULT: STROKE PREVENTION IN 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.

DOSING RECOMMENDATIONS

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 15mg once daily.

Patients with renal impairment:

In patients with moderate (creatinine clearance 30-49ml/min) or severe (15-29ml/min) renal impairment the recommended dose is 15mg once daily. BANORIV® 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 < 15ml/min.

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

Duration of therapy:

BANORIV® should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Missed dose:

If a dose is missed the patient should take BANORIV® 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 with stent placement:

There is limited experience of a reduced dose of 15mg BANORIV® once daily (or 10mg BANORIV® once daily for patients with moderate renal impairment [creatinine clearance 30-49ml/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.

Patients undergoing cardioversion:

BANORIV® can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, BANORIV® treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation.

ORAL INTAKE

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

The crushed BANORIV® 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 BANORIV® 15mg or 20mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, BANORIV® 15/20mg 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 due to BANORIV® should be assessed against the urgency of the intervention.

BANORIV® should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

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 may be increased by:

- post-operative use of indwelling epidural catheters;
- concomitant use of medicinal products affecting haemostasis;
- 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 15mg or 20mg BANORIV® in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of BANORIV® and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of BANORIV®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of BANORIV® 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 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). 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 BANORIV® is to be delayed for 24 hours.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO BANORIV®

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Banoriv therapy should be initiated when the International Normalized Ratio (INR) is ≤ 3.0.

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

CONVERTING FROM BANORIV® TO VKA

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

In patients converting from Banoriv to VKA, 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, as guided by INR testing.

Converting from parenteral anticoagulants to Banoriv

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Banoriv 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Banoriv to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next Banoriv dose would be taken.

CONTRAINDICATIONS

Like all anticoagulants, BANORIV® may increase the risk of bleeding. Therefore, BANORIV® 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 BANORIV® 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.

BANORIV® is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with BANORIV®
- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy

SPECIAL POPULATIONS

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 done after assessment of treatment benefit against the risk of bleeding:

• **Patients with renal impairment:** See “dosing recommendations” section for patients with renal impairment

• **Patients concomitantly receiving other medicinal products:**

- Use of BANORIV® is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)

- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

• **Patients with other haemorrhagic risk factors:**

As with other antithrombotics, BANORIV® 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 prosthetic valves:**

Safety and efficacy of BANORIV® have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that BANORIV® provides adequate anticoagulation in this patient population. Treatment with BANORIV® is not recommended for these patients.

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg BANORIV® and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving BANORIV®, the next BANORIV® administration should be delayed or treatment discontinued as appropriate.

Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the above measures, administration 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 BANORIV®. Due to the high plasma protein binding BANORIV® is not expected to be dialysable

COAGULATION TESTING

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

Anti-Factor Xa assays with BANORIV®-(rivaroxaban) specific calibrators to measure rivaroxaban levels. 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 BANORIV®. Dosing or treatment decisions should not be based on results of INR except when converting from BANORIV® to VKA as described above.

ADULT AND CHILDREN: TREATMENT OF DVT AND PE AND PREVENTION OF RECURRENT DVT AND PE

Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (not recommended for use in haemodynamically unstable PE patients).

DOSING RECOMMENDATIONS

Adults

Adult patients are initially treated with 15mg **twice daily** for the first three weeks. This initial treatment is followed by 20mg **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

10mg 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 BANORIV® 10mg once daily, a dose of BANORIV® 20mg **once daily** should be considered.

BANORIV® 10mg is **not** recommended for the initial 6 months treatment of DVT or PE.

Paediatric population

The safety and efficacy of Banoriv in children aged 0 to 18 years have not been established. No data are available. Therefore, Banoriv is not recommended for use in children below 18 years of age.

Patients with renal impairment:

Adults

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Banoriv is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min. In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily.
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: 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.
No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min).

Duration of therapy:

Adults

The duration of therapy should be individualised after assessment of the treatment benefit against the risk for bleeding. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Missed dose:

Adults

- If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Banoriv immediately to ensure intake of 30 mg Banoriv 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.

- If a dose is missed during the once daily treatment phase, the patient should take Banoriv 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.

ORAL INTAKE

BANORIV® 15mg and 20mg tablets 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.

Adults

For patients who are unable to swallow whole tablets, a BANORIV® tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. After the administration of crushed BANORIV® 15mg or 20mg film- coated tablets, the dose should be immediately followed by food.

The crushed BANORIV® 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 BANORIV® 15mg or 20mg film- coated tablets, the dose should then be immediately followed by enteral feeding.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, BANORIV® 15/20mg 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 due to BANORIV® should be assessed against the urgency of the intervention.

BANORIV® should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- post-operative use of indwelling epidural catheters;
- concomitant use of medicinal products affecting haemostasis;
- traumatic or repeated epidural or spinal puncture.

Patients must 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 BANORIV® 15mg or

20mg tablets in adults nor with the use of BANORIV® in children in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of BANORIV® and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of BANORIV®. Placement or removal of an epidural catheter

or lumbar puncture is best performed when the anticoagulant effect of BANORIV® 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 placement/removal of an epidural catheter and based on the general PK 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 BANORIV® (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next BANORIV® dose is administered.

If traumatic puncture occurs the administration of BANORIV® is to be delayed for 24 hours.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO BANORIV®

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

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

CONVERTING FROM BANORIV® TO VKA

There is a potential for inadequate anticoagulation during the transition from Banoriv to VKA.

Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Banoriv can contribute to an elevated INR.

In patients converting from Banoriv to VKA, 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, as guided by INR testing.

- **While patients are on both Banoriv and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Banoriv. Once Banoriv is discontinued INR testing may be done reliably at least 24 hours after the last dose.**

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO BANORIV®

• Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: BANORIV® should be started at the time of discontinuation

• Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start BANORIV® 0 to 2 hours before the time of the next scheduled administration of the parenteral drug

CONVERTING FROM BANORIV® TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given at the time the next BANORIV® dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, BANORIV® may increase the risk of bleeding. Therefore, BANORIV® is contraindicated in adults:

• 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 BANORIV® 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.

BANORIV® is also contraindicated in the following situations:

• Hypersensitivity to the active substance or to any of the excipients

• During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with BANORIV®

• During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy

SPECIAL POPULATIONS

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 done after assessment of treatment benefit against the risk of bleeding:

• **Patients with renal impairment:**

For adults, see “dosing recommendations” section for patients with renal impairment

• **Patients concomitantly receiving other medicinal products:**

- Use of BANORIV® is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)

- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

- **Patients with other haemorrhagic risk factors:**

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

In adults:

- 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 prosthetic valves:**

Safety and efficacy of BANORIV® have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that BANORIV® provides adequate anticoagulation in this patient population. Treatment with BANORIV® is not recommended for these patients.

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg BANORIV® and above in adults. A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should a bleeding complication arise in a patient receiving BANORIV®, the next BANORIV® administration should be delayed or treatment should be discontinued as appropriate.

Individualised bleeding management may include:

• Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and 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 BANORIV®. Due to the high plasma protein binding BANORIV® is not expected to be dialysable.

COAGULATION TESTING

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

Anti-FXa assays with BANORIV®-(rivaroxaban) specific calibrators to measure rivaroxaban levels are 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 BANORIV®. Dosing or treatment decisions should not be based on results of INR except when converting from BANORIV® to VKA as described above.

ADULT: PREVENTION OF VTE IN ADULT PATIENTS UNDERGOIN ELECTIVE HIP OR KNEE REPLACEMENT SURGERY

DOSING RECOMMENDATIONS

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

Patients with renal impairment:

BANORIV® is to be used with caution in patients with severe (creatinine clearance 15-29ml/min) renal impairment. Use is not recommended in patients with creatinine clearance < 15ml/min (see sections 4.4 and 5.2).

Patients with mild (creatinine clearance 50-80ml/min) or moderate (creatinine clearance 30-49ml/min) renal impairment treated for prevention of VTE in adult patients undergoing elective hip or knee replacement surgery do not require a dose reduction.

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

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 BANORIV® 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.

ORAL INTAKE

BANORIV® 10mg can be taken with or without food.

For patients who are unable to swallow whole tablets, a BANORIV® tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.

The crushed BANORIV® 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.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, BANORIV® 10mg should be stopped at least 24 hours before the intervention if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

BANORIV® 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 as determined by the treating physician.

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 may be increased by:

- post-operative use of indwelling epidural catheters;
- concomitant use of medicinal products affecting haemostasis;
- 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.

To reduce the potential risk of bleeding associated with the concurrent use of BANORIV® and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of BANORIV®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of BANORIV® is estimated to be low.

However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the placement or removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours should elapse after the last administration of BANORIV® before removal of an epidural catheter (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next BANORIV® dose is administered.

If traumatic puncture occurs the administration of BANORIV® is to be delayed for 24 hours.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO BANORIV®

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

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

CONVERTING FROM BANORIV® TO VKA

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

When converting to VKA, BANORIV® and VKA should overlap 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 BANORIV®.** While patients are on both BANORIV® and VKA the **INR should be tested the next day, just before the next dose of BANORIV® (but not within 24 hours of the previous dose; any sooner and BANORIV® will interfere with the INR result).** Once BANORIV® has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO BANORIV®

• Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: BANORIV® should be started at the time of discontinuation

• Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start BANORIV® 0 to 2 hours before the time of the next scheduled administration of the parenteral drug

CONVERTING FROM BANORIV® TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given at the time the next BANORIV® dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, BANORIV® may increase the risk of bleeding. Therefore, BANORIV® 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 BANORIV® 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.

BANORIV® is also contraindicated in the following situations:

• Hypersensitivity to the active substance or to any of the excipients

• During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with BANORIV®

• During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy

SPECIAL POPULATIONS

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. In patients receiving BANORIV® for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding:

• **Patients with renal impairment:** See “dosing recommendations” section for patients with renal impairment.

- **Patients concomitantly receiving other medicinal products:**

- Use of BANORIV® is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)

- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

- **Patients with other haemorrhagic risk factors:**

As with other antithrombotics, BANORIV® 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 prosthetic valves**

Safety and efficacy of BANORIV® have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that BANORIV® provides adequate anticoagulation in this patient population. Treatment with BANORIV® is not recommended for these patients.

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg BANORIV® and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving BANORIV®, the next BANORIV® administration should be delayed or treatment discontinued as appropriate.

Individualised bleeding management may include:

• Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and 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 BANORIV®. Due to the high plasma protein binding BANORIV® is not expected to be dialysable.

COAGULATION TESTING

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

Anti-Factor Xa assays with BANORIV®-(rivaroxaban) specific calibrators to measure rivaroxaban levels. 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 BANORIV®. Dosing or treatment decisions should not be based on results of INR except when converting from BANORIV® to VKA as described above.

ADULT: USE IN CORONARY ARTERY DISEASE (CAD) AND PERIPHERAL ARTERY DISEASE (PAD)

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

DOSING RECOMMENDATIONS

Patients taking BANORIV® 2.5mg twice daily should also take a daily dose of 75-100mg acetylsalicylic acid (ASA).

Safety and efficacy of BANORIV® 2.5mg twice daily in combination with ASA plus clopidogrel/ticlopidine has only been studied in patients with recent ACS (see below).

Dual antiplatelet therapy has not been studied in combination with BANORIV® 2.5mg twice daily in patients with CAD and/or PAD.

Patients with renal impairment:

No dose adjustment is required in patients with mild renal impairment (creatinine clearance 50-80ml/min) or moderate renal impairment (creatinine clearance 30-49ml/ min). BANORIV® is to be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) and is not recommended in patients with CrCl <15ml/min.

In patients with moderate renal impairment (CrCl 30-49ml/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations, BANORIV® 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.

Missed dose:

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

ORAL INTAKE

BANORIV® 2.5mg can be taken with or without food. For patients who are unable to swallow whole tablets, a BANORIV® tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.

The crushed BANORIV® 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.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, BANORIV® 2.5mg should be stopped at least 12 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 due to BANORIV® should be assessed against the urgency of the intervention. BANORIV® should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- post-operative use of indwelling epidural catheters;
- concomitant use of medicinal products affecting haemostasis;
- traumatic or repeated epidural or spinal puncture

Patients must 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 2.5mg BANORIV® with ASA alone or with ASA plus clopidogrel or ticlopidine in these situations. To reduce the potential risk of bleeding associated with the concurrent use of BANORIV® and neuraxial (epidural/ spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of BANORIV®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of BANORIV® is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO BANORIV®

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

CONVERTING FROM BANORIV® TO VKA

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

When converting to VKA, BANORIV® and VKA should overlap 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 BANORIV®.** While patients are on both BANORIV® and VKA the **INR should be tested the next day, just before the next dose of BANORIV® (but not within 24 hours of the previous dose; any sooner and BANORIV® will interfere with the INR result).** Once BANORIV® has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO BANORIV®

•Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: BANORIV® should be started at the time of discontinuation

•Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start BANORIV® 0 to 2 hours before the time of the next scheduled administration of the parenteral drug

CONVERTING FROM BANORIV® TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given at the time the next BANORIV® dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, BANORIV® may increase the risk of bleeding. Therefore, BANORIV® 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 BANORIV® 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

• With ACS who had a prior stroke or a transient ischaemic attack (TIA) and are receiving antiplatelet therapy

Also, concomitant treatment of CAD/PAD with BANORIV® 2.5mg and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month.

BANORIV® is also contraindicated in the following situations:

• Hypersensitivity to the active substance or to any of the excipients

• During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with BANORIV®

• During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy.

SPECIAL POPULATIONS

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. Use in these patients should be balanced against the benefit in terms of prevention of atherothrombotic events. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

- **Patients with CAD/PAD:**

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

- **Patients with renal impairment:** See “dosing recommendations” section for patients with renal impairment

- **Patients concomitantly receiving other medicinal products:**

- Use of BANORIV® is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)

- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

- Patients being treated for CAD or PAD with BANORIV® and ASA should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk

- **Patients with other haemorrhagic risk factors:**

As with other antithrombotics, BANORIV® 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 prosthetic valves:**

Safety and efficacy of BANORIV® have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that BANORIV® provides adequate anticoagulation in this patient population. Treatment with BANORIV® is not recommended for these patients

- **BANORIV® should be used with caution in CAD/PAD patients:**

BANORIV® 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 (<60kg)

- In CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with BANORIV®. (See section 5.1 of the SmPC for further clarification)

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg BANORIV® and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving BANORIV®, the next BANORIV® administration should be delayed or treatment discontinued as appropriate.

Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and 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 BANORIV®. Due to the high plasma protein binding BANORIV® is not expected to be dialysable.

COAGULATION TESTING

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

Anti-Factor Xa assays with BANORIV®-(rivaroxaban) specific calibrators to measure rivaroxaban levels. 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 BANORIV®. Dosing or treatment decisions should not be based on results of INR except when converting from BANORIV® to VKA as described above.

ADULT: USE IN ACSsp (ACUTE CORONARY SYNDROME SECONDARY PREVENTION)

Prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine.

DOSING RECOMMENDATIONS

The recommended dose of BANORIV® is 2.5mg **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.

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

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

Patients with renal impairment:

BANORIV® is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29ml/min), as limited clinical data indicates a significantly increased plasma concentration, consequently increasing bleeding risk. Use is not recommended in patients with creatinine clearance <15ml/min. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80ml/min) or moderate renal impairment (creatinine clearance 30-49ml/min).

In patients with moderate renal impairment (creatinine clearance 30-49ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations BANORIV® 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.

Missed dose:

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

ORAL INTAKE

BANORIV® 2.5mg can be taken with or without food. For patients who are unable to swallow whole tablets, a BANORIV® tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.

The crushed BANORIV® 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.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, BANORIV® 2.5mg should be stopped at least 12 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 due to BANORIV® should be assessed against the urgency of the intervention.

BANORIV® should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- post-operative use of indwelling epidural catheters;
- concomitant use of medicinal products affecting haemostasis;
- traumatic or repeated epidural or spinal puncture

Patients must 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 2.5mg BANORIV® with ASA alone or with

ASA plus clopidogrel or ticlopidine in these situations. To reduce the potential risk of bleeding associated with the concurrent use of BANORIV® and neuraxial (epidural/ spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of BANORIV®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of BANORIV® is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO BANORIV®

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

CONVERTING FROM BANORIV® TO VKA

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

When converting to VKA, BANORIV® and VKA should overlap 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 BANORIV®. While patients are on both BANORIV® and VKA the INR should be tested the next day, just before the next dose of BANORIV® (but not within 24 hours of the previous dose; any sooner and BANORIV® will interfere with the INR result).** Once BANORIV® has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO BANORIV®

• Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: BANORIV® should be started at the time of discontinuation

• Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start BANORIV® 0 to 2 hours before the time of the next scheduled administration of the parenteral drug

CONVERTING FROM BANORIV® TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given at the time the next BANORIV® dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, BANORIV® may increase the risk of bleeding. Therefore, BANORIV® 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 BANORIV® 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

• With ACS who had a prior stroke or a transient ischaemic attack (TIA) and are receiving antiplatelet therapy

BANORIV® is also contraindicated in the following situations:

• Hypersensitivity to the active substance or to any of the excipients

• During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with BANORIV®

• During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy

SPECIAL POPULATIONS

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.

Use in these patients should be balanced against the benefit in terms of prevention of atherothrombotic events. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

• **Patients with renal impairment:** See “dosing recommendations” section for patients with renal impairment

• **Patients concomitantly receiving other medicinal products:**

- Use of BANORIV® is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)

- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

- After an acute coronar syndrome patients on treatment with BANORIV® and ASA or BANORIV® 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)

• **Patients with other haemorrhagic risk factors:**

As with other antithrombotics, BANORIV® 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 prosthetic valves:**

Safety and efficacy of BANORIV® have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that BANORIV® provides adequate

anticoagulation in this patient population. Treatment with BANORIV® is not recommended for these patients.

- **BANORIV® should be used with caution in ACS patients.**

BANORIV®, co-administered with ASA alone 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 (<60kg)

- Concomitant treatment of ACS with BANORIV® and antiplatelet therapy

is contraindicated in patients with a prior stroke or a transient ischaemic attack (TIA)

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg BANORIV® and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving BANORIV®, the next BANORIV® administration should be delayed or treatment discontinued as appropriate.

Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and 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 BANORIV®. Due to the high plasma protein binding BANORIV® is not expected to be dialysable

COAGULATION TESTING

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

Anti-Factor Xa assays with BANORIV®-(rivaroxaban) specific calibrators to measure rivaroxaban levels. 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 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 activity of BANORIV®. Dosing or treatment decisions should not be based on results of INR except when converting from BANORIV® to VKA as described above.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Reporting of Side effects: Adverse events can be reported to:

- SFDA-National Pharmacovigilance and Drug Safety Center
  - **Email:** npc.drug@sfda.gov.sa
  - **Website:** http://ade.sfda.gov.sa
  - **Unified number:** 19999
- SPIMACO Company
  - **Email:** GPV@spimaco.sa
  - **Tel:** +966 11 2523393