Rivaroxaban Sandoz ▼

10 mg, 15 mg and 20 mg Film-coated tablets

PRESCRIBER'S GUIDE

Patient Alert Card

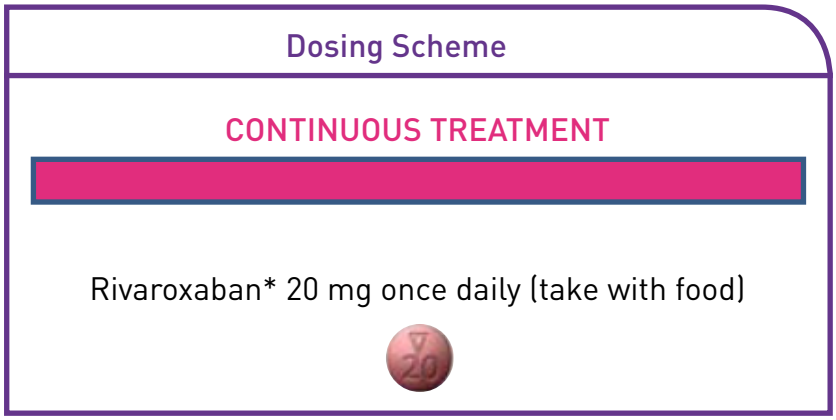
A patient alert card must be provided to each patient who is prescribed rivaroxaban 10 mg, 15 mg or 20 mg and is provided with the product package. The implications of anticoagulant treatment should be explained. Specifically, the need for compliance, the need to take with food and signs of bleeding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

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

Dosing Recommendations

Dosing in patients with atrial fibrillation

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation is 20 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. Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15 – 29 ml/min). Use is not recommended in patients with creatinine clearance < 15 ml/min.

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

Duration of therapy:

Rivaroxaban 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 Rivaroxaban immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Patients with non-valvular atrial fibrillation undergoing PCI with stent placement:

There is limited experience of a reduced dose of 15 mg Rivaroxaban once daily (or 10 mg Rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30-49 ml/min]) in addition of 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:

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

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

Dosing in treatment of deep vein thrombosis (DVT}, pulmonary embolism (PE} and prevention of recurrent DVT and PE in adults.

Patients are initially treated with 15 mg 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 Rivaroxaban 10 mg **once daily**, a dose of Rivaroxaban 20 mg **once daily** should be considered.

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

DOSING SCHEME

Initial Treatment	Day 22 onwards	Following completion of at least 6 months
Rivaroxaban 15 mg twice daily* 	Rivaroxaban 20 mg once daily* 	Rivaroxaban 10 mg once daily*  Rivaroxaban 20 mg once daily*  Dose adaptation to 10 mg once daily based on individual assessment of the risk of recurrent DVT/ PE against the risk for bleeding

10 mg: take with or without food

15/20 mg: must be taken with food

* Recommended dosing scheme for patients with DVT/PE and moderate or severe renal impairment see above.

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 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 PK modeling and has not been studied in this clinical setting. Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 ml/ min). The use of Rivaroxaban is not recommended in patients with creatinine clearance < 15 ml/min. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

Duration of therapy:

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE

Missed dose

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

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

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

Duration of treatment:

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopedic 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 Rivaroxaban immediately and then continue the following day with once daily intake as before.

Oral Intake

Rivaroxaban 10 mg can be taken with or without food.

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

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

The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

Perioperative Management

If an invasive procedure or surgical intervention is required,

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

if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

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

Spinal/epidural anesthesia or puncture

When neuraxial anesthesia (spinal/epidural anesthesia) 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 hematoma 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 hemostasis. 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.

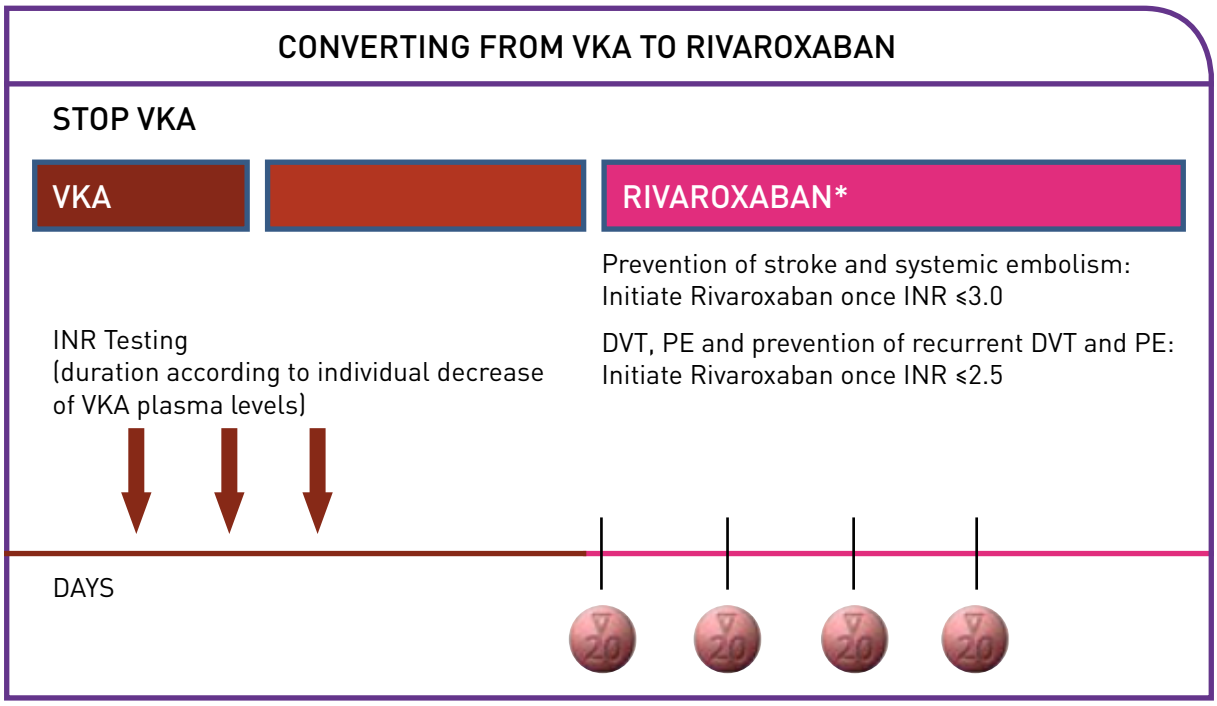
For indication specific recommendations please refer to the sections below:

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF) Treatment of DVT and PE and prevention of recurrent DVT and PE in adults Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

There is no clinical experience with the use of 10/15/20 mg Xareltoin these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

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

Converting from VKA to Rivaroxaban



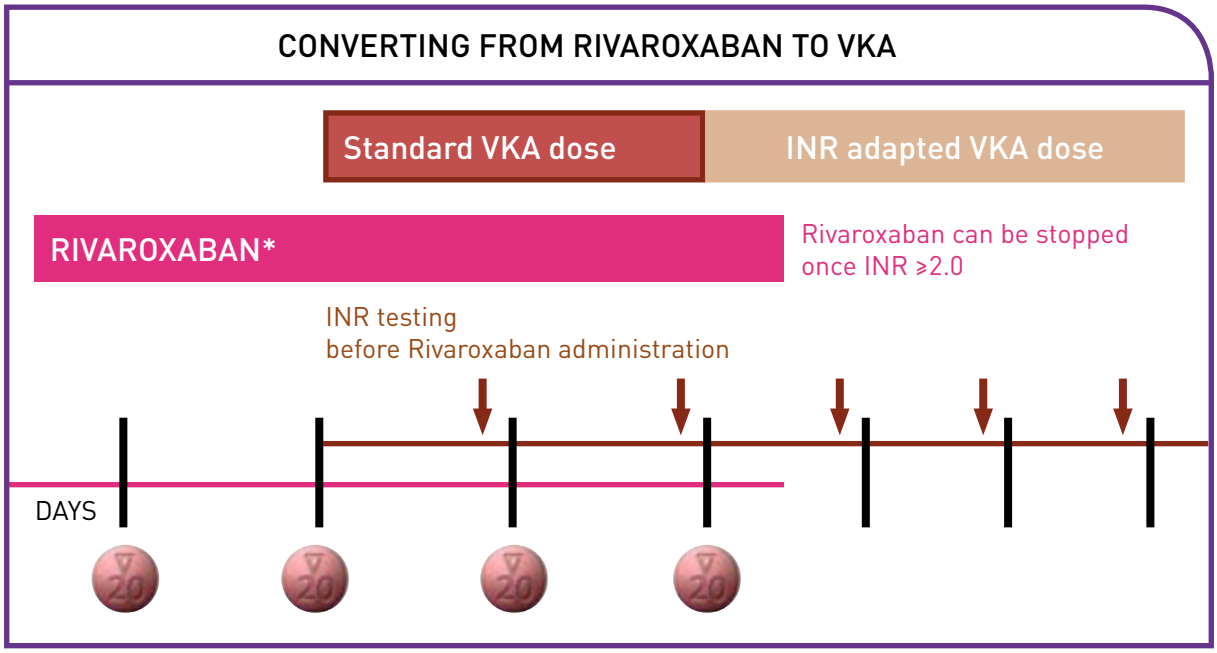
*See dosing recommendations for required daily dose

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

For patients treated for DVT, PE and prevention of recurrent DVT and PE, treatment with VKA should be stopped and Rivaroxaban therapy should be initiated when the INR is ⩽ 2. For patients treated for prevention of stroke and systemic embolism, treatment withVitamin K Antagonists (VKA) should be stopped and Rivaroxaban therapy should be initiated when the INR is ⩽ 3.0.

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

Converting from Rivaroxaban to VKA



*See dosing recommendations for required daily dose

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

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

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

Converting from Parenteral Anticoagulants to Rivaroxaban

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

Converting from Rivaroxaban to Parenteral Anticoagulants

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

Populations Potentially at Higher Risk of Bleeding

Like all anticoagulants, Rivaroxaban may increase the risk of bleeding

Therefore Rivaroxaban is contraindicated in patients

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

Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications and anemia after initiation of treatment with Rivaroxaban . In patients receiving Rivaroxaban 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 hemoglobin. Any unexplained fall in hemoglobin 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 for bleeding:

- Patients with renal impairment: See "dosing recommendations" for patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment. Rivaroxaban is to be used with caution in patients with creatinine clearance (15-29 ml/min) and in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations. Use of Rivaroxaban is not recommended in patients with creatinine clearance <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 Rivaroxaban is not recommended
  - Care is to be taken in patients concomitantly receiving drugs affecting hemostasis such as NSAIDs, acetylsalicylic acid or platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
  - After an acute coronary syndrome patients on treatment with Rivaroxaban and ASA or Rivaroxaban and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
  - Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin). Patients with other hemorrhagic risk factors

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

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

Other contraindications

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

Overdose

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

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

Individualized bleeding management may include

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Hemodynamic 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 Rivaroxaban.

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

Coagulation Testing

Rivaroxaban does not require routine coagulation monitoring. However, measuring Rivaroxaban levels may be useful in exceptional situations where knowledge of Rivaroxaban exposure may help to take clinical decisions,

e.g. overdose and emergency surgery.

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

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

▼ 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.

Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and posted to:

Medicines Authority Post-licensing Directorate, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann. SGN 3000.

Or sent by e-mail to postlicensing.medicinesauthority@gov.mt

Healthcare Professionals may also report any adverse events suspected to be associated with the use of Rivaroxaban Sandoz to Novartis Country Patient Safety, by phone on +356 21222872 or e-mail at drug_safety.malta@novartis.com.

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Local Distributor: VJ Salomone Pharma Limited – Upper Cross Road, Marsa, MRS 1542, Malta

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available at: http://www.medicinesauthority.gov.mt/advanced-search