INESSS
LE SAVOIR PREND FORME

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DRUG PRODUCT ANTICOAGULANT THERAPY WITH DABIGATRAN (PRADAX™)

ATRIAL FIBRILLATION

DESCRIPTION OF THE MEDICATION AND INDICATION

Dabigatran is a direct and specific inhibitor of thrombin, the final enzyme in the coagulation cascade. It is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) requiring anticoagulant therapy.

Warfarin remains the drug of choice given its efficacy and long-term safety, as well as its favourable cost effectiveness.

CRITERIA FOR REIMBURSEMENT BY THE RAMQ

Since April 2011, dabigatran may be reimbursed as an exceptional medication:

- in persons with non-valvular atrial fibrillation requiring anticoagulant therapy:
  - for whom anticoagulation with warfarin or nicoumalone is not within the targeted therapeutic range; or
  - for whom anticoagulation monitoring with warfarin or nicoumalone is not possible or is not available.

A patient who is not a good candidate for anticoagulation should not receive dabigatran.

POPULATIONS IN WHICH DABIGATRAN SHOULD NOT BE USED

- Patients with a history of:
  - Valvulopathy (prosthetic valve or hemodynamically relevant valve disease)
  - Poor treatment adherence (or risk thereof)
  - Severe or disabling stroke within the past six months, or any stroke within the past 14 days
- Patients with any of the following conditions:
  - Severe renal impairment (creatinine clearance [CrCl] less than 30 ml/min) or acute renal failure
  - Active liver disease or hepatic enzyme levels twice the upper limit of normal
  - Increased risk of bleeding
  - Known hypersensitivity to dabigatran or one of its components
- Children under 18 years old
- Pregnant and nursing women

When patients receiving warfarin have an international normalized ratio (INR) within the therapeutic range over 67% of the time, switching to dabigatran is not warranted.

Québec

USE OF DABIGATRAN VERSUS WARFARIN

ADVANTAGES	DISADVANTAGES
Prevention of stroke and systemic embolism	
• At the 150 mg dose, the absolute risk reduction of stroke or systemic embolism is 0.6% per year when compared with warfarin (NNT* = 167). However, the clinical significance of this superiority is debatable.	• Clinical data taken from a single study over two years • Lack of data concerning various populations, including patients with a CrCl lower than 30 ml/min and those with liver disease
Bleeding and adverse reactions	
• Fewer intracranial bleeds: 0.3% per year with the 150 mg treatment, compared with 0.74% (NNH† = 227)	• More gastrointestinal bleeds: 1.51% per year with the 150 mg treatment, compared with 1.02% (NNH† = 204) • Increased frequency of dyspepsia: 11.3% with the 150 mg treatment, compared with 5.8% (NNH† = 18) • Unknown long-term safety profile • **No specific antidote**
Pharmacokinetics	
• Fixed dosage • Fast anticoagulant effect: one to three hours • Short half-life ($T_{1/2}$): anticoagulant effect disappears more rapidly once treatment is terminated	• Must be taken twice daily • Short $T_{1/2}$: missed dose results in rapid loss of efficacy • Little data concerning patients who weigh less than 50 kg or more than 100 kg
Clinical supervision	
• INR monitoring not required	• Heightened monitoring of renal function required in the populations most at risk • No standardized laboratory test currently available to quantify the anticoagulant activity • Treatment more frequently discontinued: 16% with the 150 mg treatment, compared with 10% at one year (NNH† = 16); and 21%, compared with 17% at two years (NNH† = 25) • More problems with treatment adherence
Drug or dietary interactions	
• Not a substrate of cytochrome P450 • No interaction with foods containing vitamin K	• Limited clinical data available • Less well-known clinical impact
Stability, storage and administration	
	• Sensitive to humidity: keep in original packaging • No information on pill organizers • **The large capsule must be swallowed whole: exposure may be elevated by 75% if the capsule is opened, broken or chewed** • Use is impossible through nasogastric or Levin tube
Cost of treatment	
	• Increased monthly cost: $96.00‡, compared with $34.80§ (including INR measurement costs) on average

Source: Adapted from Dumont and Bunka, 2010

* Number Needed to Treat: The number of patients who need to be treated over a specific period of time to prevent one additional adverse outcome, as compared with another treatment
† Number Needed to Harm: The number of patients who need to be treated over a specific period of time to see one additional harmful event, as compared with another treatment
‡ Monthly cost of the medication, excluding the pharmacist's dispensing fees and the wholesaler's profit margin
§ Canadian Agency for Drugs and Technologies in Health, 2011

INITIATION AND DOSAGE OF DABIGATRAN

Prerequisite assessment: compliance, potentially harmful interactions, hepatic and renal function, and complete blood count (CBC)

A 150 mg dose of dabigatran twice daily should be privileged. This dosage is more effective for prevention of stroke and systemic embolism than warfarin or a 110 mg dose of dabigatran.

SPECIAL POPULATIONS

Renal impairment
Dabigatran is contraindicated when CrCl is lower than 30 ml/min.

Body weight
Because limited relevant data is available, dabigatran should be used with caution in patients who weigh less than 50 kg or over 100 kg.

Geriatrics
Several characteristics associated with the elderly make the use of dabigatran **risky** in this population: renal failure, polymedication, use of a pill organizer, dysphagia, cognitive impairment, low body weight and undernutrition. This population has also been underrepresented in clinical trials. As a result, dabigatran should not be prescribed without first conducting a complete assessment of its benefits and risks. In patients over the age of 80, a 110 mg dose of dabigatran may be warranted if warfarin cannot be used. The use of dabigatran requires renal function and treatment compliance to be monitored more closely.

Warfarin remains the drug of first choice for patients aged 80 or older.

LABORATORY MONITORING REQUIRED

No routine tests are available to quantitatively monitor the anticoagulant activity of dabigatran.
This leads to difficulties in emergencies, such as when bleeding is present.

Close monitoring of renal function is required because of its role in the excretion of dabigatran. It is recommended that **CrCl be calculated at least twice per year and as needed,** according to changes in the patient's drug profile (e.g., NSAID, ACEIs) or medical condition (e.g., dehydration, bleeding).

INTERRUPTION OF DABIGATRAN IN PATIENTS UNDERGOING ELECTIVE INTERVENTION

1- Determine the risk of bleeding associated with the intervention

INTERVENTIONS WITH A STANDARD RISK OF HEMORRHAGE	INTERVENTIONS WITH A HIGH RISK OF HEMORRHAGE OR WHERE COMPLETE HEMOSTASIS MAY BE REQUIRED
• Colonoscopy with polypectomy • Laparoscopic cholecystectomy • Angiography • Major orthopedic surgery • Pacemaker insertion	• Cardiac or abdominal surgery, surgery of the prostate/ bladder, neurosurgery, renal biopsy or surgery involving a vital organ • Other procedures such as spinal anaesthesia (complete hemostasis required)

The nature of dental work varies, as does the risk of hemorrhage associated with each procedure. Discuss the risk of bleeding associated with a particular procedure with the dentist.

Cataract surgery performed under topical anesthesia, without a retrobulbar block, usually presents little risk of bleeding and should not require an interruption of anticoagulation. Likewise for certain rheumatologic procedures (e.g., arthrocentesis/joint injections of the shoulder and knee) that pose few problems since they have a low risk of bleeding and any hemorrhage would have minor consequences.

2- Discontinue dabigatran before elective intervention based on the risk of hemorrhage and state of renal function

RENAL FUNCTION (CrCl, ml/min)	TIME BETWEEN INTERVENTION AND THE LAST DOSE OF DABIGATRAN	
	Intervention with a **standard** risk of hemorrhage	Intervention with a **high** risk of hemorrhage
50 or higher	24 hours	2-4 days
30 to 49	48 hours	4 days
Less than 30	2-5 days	More than 5 days

* When appropriate, resume dabigatran only if the CrCl is 30 ml/min or higher.

3- Assess the degree of anticoagulation in patients with a high risk of hemorrhage

Test the activated cephalin time (ACT)
Normal ACT: lack of clinically significant anticoagulant effect; elevated ACT: according to an analysis of the risks and benefits, intervention may be postponed; ACT of 80 seconds or more: high anticoagulant effect, intervention should be postponed.

In the case of an emergency intervention, estimate the length of residual exposure to dabigatran, obtain the time of last dose of dabigatran, calculate the CrCl and analyze the risks and benefits of the intervention, by the interpretation of the ACT value.

RESUMPTION OF DABIGATRAN

The resumption of dabigatran, if the CrCl is 30 ml/min or higher, depends on the risk of postoperative bleeding. When risk of bleeding is low, dabigatran is generally resumed 24 hours after the procedure. When risk of bleeding is elevated, dabigatran is resumed 48 hours after the procedure.

SWITCHING FROM ANOTHER ANTICOAGULANT TO DABIGATRAN

DRUG PRODUCT AND ROUTE OF ADMINISTRATION	PRECAUTIONS
Unfractioned heparin administered through continuous IV infusion	Stop the heparin infusion and start dabigatran immediately.
Unfractioned heparin or low-molecular-weight heparin administered subcutaneously	Start dabigatran two hours before the last scheduled dose of heparin, and discontinue heparin treatment permanently.
Vitamin K antagonist (VKA) administered orally	Stop VKA and start dabigatran when the INR is lower than 2.0.

SWITCHING FROM DABIGATRAN TO A PARENTERAL ANTICOAGULANT

CrCl (ml/min)	PRECAUTIONS
30 or higher	Start heparin 12 hours after the last dose of dabigatran.
Lower than 30	Start heparin 24 hours after the last dose of dabigatran. When appropriate, resume dabigatran only if the CrCl is 30 ml/min or higher.

Heparin may be started earlier depending on the clinical situation, such as in the case of pulmonary embolism or acute coronary syndrome.

SWITCHING FROM DABIGATRAN TO A VITAMIN K ANTAGONIST

CrCl (ml/min)		HALF-LIFE (HOURS)	PRECAUTIONS
50 or higher	80 or higher	13 (11-22)	Start VKA three days before stopping dabigatran.
	50 to 79	15 (12-34)	
30 to 49		18 (13-23)	Start VKA two days before stopping dabigatran.
Lower than 30		27 (22-35)	Stop dabigatran, estimate its $T_{1/2}$ and start VKA according to clinical opinion. Where relevant, resume dabigatran only if the CrCl is 30 ml/min or higher.

DRUG MONITORING

Treatment adherence

Monitoring treatment adherence is important. Discontinuation of treatment with dabigatran occurs more often with patients having dyspepsia. In addition, dabigatran must be taken regularly twice daily, at intervals of about 12 hours.

Adverse reactions

Warfarin and the 150 mg dose of dabigatran carry the same risk of major bleeding. In patients being treated with dabigatran, gastrointestinal bleeding is more frequent, while intracranial bleeding is less frequent.

Only the 110 mg dose is associated with a statistically significant reduction in the incidence of major bleeding compared with warfarin. However, other factors that increase the risk of hemorrhage must be considered.

Gastrointestinal disorders caused by dabigatran are twice as many as those caused by warfarin. Eating can reduce epigastric pains.

Advice to patients

- Inform all health professional that you are taking dabigatran.
- Consult a physician in case of prolonged or excessive bleeding, or in case of accidental overdose, even if you have no symptoms.
- Consult a pharmacist before taking any natural health product or any prescription or non-prescription drug product.
- Always wear a bracelet that indicates your use of dabigatran.

If you forget a dose, take the missed dose up to six hours before the next scheduled dose. Do not double the dose.

Drug interactions (prescription or non-prescription drug products)

There are presently few documented interactions with dabigatran. Exercise caution when changes to the drug profile are made.

EFFECT ON DABIGATRAN	MECHANISM	DRUG PRODUCT	FINDINGS AND PRACTICES KNOWN TO DATE
Increased blood concentration of dabigatran	P-glycoprotein (P-gp) inhibition*	Ketoconazole	• This combination is contraindicated.
		Clarithromycin	Little clinical data, and complex interaction mechanism: • No dose adjustment recommended. • Consider a different antibiotic treatment.
		Verapamil	• Administer dabigatran two hours before verapamil.
		Amiodarone	Exposure to dabigatran is increased by 60%. The effect on the risk of bleeding is less well-known: • No dose adjustment has been clearly established.
Decreased blood concentration of dabigatran	Complex mechanism (also involving P-gp)	Atorvastatin	Little clinical data; concentrations of dabigatran are decreased by about 20 %. Little data on other statins: • No dose adjustment recommended.
	P-gp induction†	Rifampicin	• This combination should be avoided.
	Reduced absorption due to changes in pH	Antacids‡ and H_2 antagonists	• Administer dabigatran two hours before the antacid.
		PPIs	**Decreased exposure to dabigatran by 11% to 30% has been reported:** • **No dose adjustment recommended.**
Increased risk of bleeding	Possible pharmacodynamic interaction	Diclofenac and other NSAIDs	• Analyze the risks and benefits. • Avoid this combination where possible.
		ASA, clopidogrel	• Avoid this combination where possible.

* Other P-gp inhibitors that may increase serum concentrations of dabigatran are dronedarone, tamoxifen, azithromycin, erythromycin, grapefruit juice, lovastatin, simvastatin, ritonavir, itraconazole, cyclosporin, tacrolimus, paroxetine and spironolactone. Use with caution.
† Other P-gp inducers that may reduce serum concentrations of dabigatran are St. John's wort, tenofovir, phenytoin, carbamazepine, phenobarbital and dexamethasone. Use with caution.
‡ Aluminum compounds, sodium bicarbonate, calcium and/or magnesium compounds or a combination thereof.

OVERDOSAGE

- Administer activated charcoal if dabigatran was ingested within the past two hours and if administration is not otherwise contraindicated.
- Contact the Québec Poison Control Centre (Centre antipoison du Québec) immediately, at 1-800-463-5060.
- Consider that several products may have been ingested.
- Consider that the capsules may have been opened or broken, resulting in increased exposure to dabigatran.

DRUG PRODUCT
DABIGATRAN (PRADAX™)

CLINICAL MANAGEMENT OF BLEEDING IN PATIENTS TREATED WITH DABIGATRAN

There is no product that reverses the effect of dabigatran.

All types of bleeding

- Time of last dose of dabigatran
- Laboratory tests:
  - Creatinine
  - CBC
  - ACT*
  - Fibrinogen
- Skip 1 to 2 doses
- Local control: mechanical compression

CrCl: Use to estimate the $T_{1/2}$ of dabigatran, i.e., the length of its effect *in vivo*.

CBC: Use to diagnose thrombocytopenia and measure a baseline hemoglobin (Hb) level.

ACT*: Increased under dabigatran.

Fibrinogen: Dosage helps confirm the absence of a disseminated intravascular coagulation (DIVC).

Moderate or serious bleeding

Supportive treatment:

- Surgical intervention
- Hemodynamic support and blood volume repletion
- Blood products transfusion depending on the condition
- Preservation of diuresis to promote elimination of dabigatran
- Administration of desmopressin if antiplatelet therapy is being used
- Administration of cryoprecipitate and/or platelets if DIVC/fibrinogen is 1.5 g/l or lower
- Consider hemodialysis

Reconsider the indication for anticoagulants

Platelets in case of thrombocytopenia; packed red blood cells in case of low Hb

Serious and potentially fatal bleeding

Supportive treatment:

- Consider hemodialysis (recommendation based on similar drug products)

Fresh frozen plasma and **prothrombin complex concentrates** are not effective in reversing the effects of dabigatran. The latter also carry a thrombogenic risk. Use with caution.

Source: Adapted from the *Journal of Thrombosis and Haemostasis*, 2010, University of Utah Health Care Thrombosis Service

LABORATORY TESTS

* ACT is the most useful follow-up test for patients taking dabigatran. Normal results indicate the lack of a clinically significant anticoagulant effect. Elevated results indicate significant anticoagulation but do not quantify the anticoagulant effect.

Thrombin time (TT) is very sensitive to the presence of dabigatran: it can remain elevated for long periods, despite low blood concentrations. Normal TTs exclude the presence of dabigatran in the blood. Elevated results indicate significant anticoagulation but do not quantify the anticoagulant effect.

The INR is not sensitive to the effect of dabigatran: its measurement is not correlated with plasma concentrations.

Sensitive and specific coagulation tests are currently being evaluated.

MAIN REFERENCES

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