Pradaxa 75 mg capsules	Updated Patient Information Leaflet
Boehringer Ingelheim	June 2020

Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is to be supplied by physician's prescription only

Pradaxa® 75 mg Capsules

Active ingredient:
Each capsule of **Pradaxa 75** contains: 75 mg dabigatran etexilate (as mesilate)

Inactive ingredients and allergens in the medicine - See section 6.

Read the entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about this medicine. If you have any further questions, ask your physician or the pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar.

Patient information card:
This card contains important safety information which you should know prior to beginning treatment with Pradaxa and during the treatment with Pradaxa.
The card contains information intended for both the patient and the healthcare staff. It provides guidance for the patients on how to minimize the risk of bleeding resulting from treatment with any anticoagulant agent.
In addition, the card contains personal details of the patient and information regarding Pradaxa for the healthcare staff.
Present this card to any healthcare professional involved in your treatment.

1. What is this medicine intended for?

Pradaxa contains the active ingredient dabigatran etexilate that belongs to a group of medicines called anticoagulants. Pradaxa is intended for prevention of thrombosis of the veins following elective knee replacement or hip replacement orthopedic surgeries in adults.

Therapeutic group: Anticoagulants.

2. Before using this medicine

Do not use this medicine if:

- ☒ You are sensitive (allergic) to the active ingredient or to any of the other ingredients that this medicine contains (for the list of inactive ingredients, see section 6).
- ☒ You suffer from severe renal impairment.
- ☒ You suffer from active bleeding.
- ☒ You suffer from any disease in any of the body organs, which may increase the risk of severe bleeding (such as stomach ulcer, injury or bleeding in the brain, or if you have recently had surgery of your brain or eyes).
- ☒ You have an increased risk of bleeding due to an inborn factor or use of other medicines or due to an unknown reason.
- ☒ You are taking other anticoagulants, such as: warfarin (known as Coumadin), rivaroxaban, apixaban or heparin unless when the anticoagulant treatment has been changed, during insertion of a venous or arterial catheter while you receive heparin through it to maintain it open, or during a medical procedure called catheter ablation to regulate your heart rate following atrial fibrillation.
- ☒ You suffer from significant impairment of liver function or a liver disease that may be life-threatening.
- ☒ You are taking oral ketoconazole or itraconazole, medicines for the treatment of fungal infection.

- ☒ You are taking oral cyclosporine, a medicine used for the prevention of transplant rejection.
- ☒ You are taking dronedarone, a medicine used to treat abnormal heart beat.
- ☒ You are taking a combined agent containing glecaprevir and pibrentasvir, an antiviral medicine used to treat viral hepatitis C.
- ☒ An artificial valve has been implanted in your heart, so you require permanent blood thinning.

Special warnings about using this medicine

Consult your physician prior to taking Pradaxa. You may also need to consult your physician during the period of treatment with Pradaxa if you experience symptoms or have to undergo surgery.

Lesions, medical conditions or medication therapies (such as: non-steroidal anti-inflammatory drugs, e.g. Nurofen or Advil, anti-platelet agents e.g. aspirin, antidepressants and anti-anxiety drugs of the SSRI or SNRI groups) may significantly increase the risk of bleeding, thus requiring risk – benefit assessment by the physician. If you are older than 75 years or have impaired renal function or concomitantly use medications such as verapamil (hypertension), amiodarone (arrhythmias) or ticagrelor (for the reduction of risk of cardiovascular events), or their combination, the physician will recommend treatment with Pradaxa only if the benefit outweighs the risk of bleeding.

Before using Pradaxa tell your physician:

Before taking Pradaxa, tell the physician if you have or have ever had any diseases and medical conditions, in particular those listed below:

- If you are at increased risk of bleeding, for example:
  - If you have recently suffered from bleeding.
  - If you have undergone a biopsy in the last month.
  - If you have recently suffered a serious injury (such as bone fracture, head injury or any injury requiring surgical treatment).
  - If you suffer from inflammation in the esophagus or stomach.
  - If you suffer from reflux or a problem associated with penetration of gastric juice to the esophagus.
  - If you are taking medicines increasing the risk of bleeding (see section 'Other Medicines and Pradaxa', below).
  - If you are taking anti-inflammatory drugs such as diclofenac, ibuprofen, piroxicam.
  - If you suffer from infection in the heart (bacterial endocarditis).
  - If you know that you have reduced renal function, or if you suffer from dehydration (symptoms include thirst and decreased urination; the urine may become dark colored (concentrated)).
  - If you are older than 75 years.
  - If your weight is 50 kg or less.
- If you have suffered a heart attack or have been diagnosed with increased risk of developing a heart attack.
- If you suffer from a liver disease causing changes in your blood tests, the use of Pradaxa is not recommended.

Take special care with Pradaxa:

- If you are required to undergo surgery:
  In such a case, you will have to stop taking Pradaxa temporarily due to the risk of increased bleeding during the surgery and for a short period of time after it. It is very important to take Pradaxa before and after surgery exactly at the times you have been told by your physician.
- If the surgery involves inserting a catheter or injection into your spinal column (for example, for epidural or spinal anesthesia or pain reduction):
  - It is very important to take Pradaxa before and after surgery exactly at the times you have been told by your physician.
  - Tell your physician immediately if you get numbness or weakness in your legs or problems with your bowels or bladder after the end of anesthesia, because you may need immediate care.

- If you fall or get injured during the treatment, especially if you experience a head trauma, please seek urgent medical treatment. You may need to be examined by a physician since you may be at increased risk of bleeding.
- If you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of forming blood clots), tell your physician who will decide if the treatment may need to be changed.

Children and adolescents
The medicine is not recommended for children and adolescents under 18 years old.

Other medicines and Pradaxa
If you are taking or have recently taken other medicines, including nonprescription medications and nutritional supplements, inform your physician or pharmacist. Particularly, tell your physician or pharmacist if you are taking the following medicines (note that the following list indicates the active ingredients contained in the medicines. If you are not sure whether you use any of these medicines, please consult your physician or pharmacist):

- Medicines for reducing excessive blood coagulation (such as warfarin, phenprocoumon, acenocoumarol, heparin, clopidogrel, ticagrelor, prasugrel, rivaroxaban, acetylsalicylic acid)
- Medicines to treat fungal infections (such as ketoconazole, itraconazole), unless they are only applied to the skin
- Medicines to treat abnormal heart beats (such as amiodarone, dronedarone, quinidine, verapamil). If you are taking medicines that contain amiodarone, quinidine or verapamil, your physician will tell you to use a reduced dose of Pradaxa. See section 3: 'How to Use this Medicine'
- Medicines to prevent organ rejection after transplantation (such as tacrolimus, cyclosporine)
- A combined agent containing glecaprevir and pibrentasvir, an antiviral medicine used to treat viral hepatitis C
- Analgesics and anti-inflammatory medicines (such as acetylsalicylic acid, ibuprofen, diclofenac)
- Medicines containing hypericum (St. John's Wort), a herb used for the treatment of depression
- Antidepressants of the group of selective serotonin/noradrenaline reuptake inhibitors (SSRI or SNRI)
- Rifampicin or clarithromycin antibiotics
- Medicines for the treatment of AIDS/HIV (such as ritonavir)
- Certain medicines for the treatment of epilepsy (such as carbamazepine, phenytoin)

Using the medicine and food
The medicine can be taken regardless of meal times. The capsule should be swallowed whole with a glass of water, to ensure its delivery to the stomach. Do not break, chew, or empty the contents of the capsule. This is to prevent an increase in the risk of bleeding.

Pregnancy, breastfeeding, and fertility
The effect of Pradaxa on pregnancy and the fetus is unknown. Do not use the medicine if you are pregnant unless the physician recommended it to you and determined that it is safe. If you are a woman of childbearing age, avoid getting pregnant during treatment with Pradaxa. Do not breastfeed during the treatment with Pradaxa.

Driving and using machines
Pradaxa has no known effect on driving or using machines.

3. How to use this medicine?

Always use according to the physician's instructions. Check with your physician or pharmacist if you are not sure about the dosage or how to use the medicine. Only your physician can determine your dose and how you should take the medicine. **Do not exceed the recommended dose.**

The recommended dose is usually:
The recommended dose is **220 mg once a day** (taken as 2 capsules of 110 mg).

- If your **kidney function is impaired** by more than half of its normal function or you are **older than 75 years,** the recommended dose of Pradaxa is **150 mg once a day** (taken as 2 capsules of 75 mg).
- If you are taking **medicines that contain amiodarone, quinidine, or verapamil,** the recommended dose is **150 mg once a day** (taken as 2 capsules of 75 mg).
- If you are taking medicines containing verapamil, and your kidney function is impaired by more than half of its normal function, your dose must be reduced to **75 mg** of Pradaxa because you may have a higher risk of bleeding.

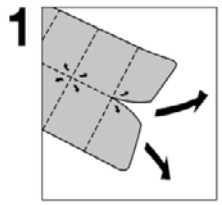
For both types of surgery, do not start treatment with Pradaxa if you are actively bleeding from the surgical site. If you cannot start treatment until the day after surgery, start treatment with two capsules once a day.

After knee-replacement surgery
you must begin treatment with Pradaxa within 1-4 hours after surgery; start with one capsule. Continue after that with two capsules once a day until you complete 10 days.

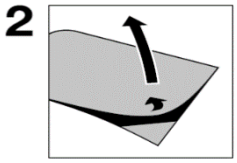
After hip-replacement surgery
you must begin treatment with Pradaxa within 1-4 hours after surgery; start with one capsule. Continue after that with two capsules once a day until you complete 28-35 days.

Instructions for opening the blisters:

The following figures illustrate how to take Pradaxa capsules out of the blister pack:



Tear off one individual blister from the blister card along the perforated line.



Peel off the blister foil and remove the capsule.

- Do not push the capsules through the aluminum foil.
- Do not peel off until a capsule is required.
- Swallow the capsule whole with a glass of water, regardless of meals. Do not break, chew, or empty the contents of the capsule. This is to prevent an increase in the risk of bleeding.

Changing anticoagulant treatment

Do not change your anticoagulant treatment without specific guidance from your physician.

If you have accidentally taken a higher dose:
Taking an overdose of Pradaxa may increase the risk of bleeding. If you have taken an overdose notify your physician immediately. Specific treatment options are available.

If you forget to take the medicine:
Take the next dose of Pradaxa on the next day at the usual time. Do not take a double dose to make up for the missed dose.
Persist with the treatment as recommended to you by the physician.

If you stop taking the medicine:
Take Pradaxa exactly as prescribed by the physician. Do not stop taking Pradaxa without consulting your physician, because the risk of developing a blood clot could be higher if you stop the treatment too early.

Do not take medicines in the dark! Check the label and dose each time you take the medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your physician or the pharmacist.

4. Side effects

Like all medicines, taking Pradaxa may cause side effects in some users. If the side effects persist or are bothersome, or if they get worse, consult your physician. Do not be alarmed by this list of side effects. You may not experience any of them.

Contact your physician immediately in the following cases:

- Pradaxa affects blood clotting; therefore most of the side effects are associated with signs such as bruising or bleeding. Significant bleeding events may occur. These are the most serious side effects, which regardless of the site of bleeding, may lead to disability, may be life threatening and even fatal. In some cases, these bleeding events are not visible.
- If you suffer from bleeding which does not resolve spontaneously or if you experience symptoms of massive bleeding (unusual weakness, tiredness, pallor, dizziness, headaches or unexplained swelling), consult the physician immediately. Your physician may decide to keep you under observation or change the medicine.
- If you experience a severe allergic reaction causing difficulty breathing or dizziness.

The potential side effects listed below have been classified according to their frequencies:

Common side effects (affect 1-10 in 100 users):

- A fall in the amount of hemoglobin in the blood
- Abnormal liver function in laboratory tests.

Uncommon side effects (affect 1-10 in 1000 users):

- Nosebleed, bleeding in the stomach or bowels, vaginal/penile bleeding, urinary tract bleeding (including blood in the urine coloring it to pink or brown), hemorrhoidal bleeding, anal bleeding, subcutaneous bleeding, bleeding into a joint, from or after an injury or postoperative bleeding
- Hematoma or bruises on the skin (blue spots on the skin) after surgery
- Fecal occult blood discovered in laboratory test
- Decrease in the number or percentage of red blood cells
- Allergic reaction
- Vomiting
- Frequent or liquid stools
- Nausea
- Fluid exiting a wound (fluid discharge from the surgical wound)
- Liver enzymes increased
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems.

Rare side effects (affect 1-10 in 10000 users):

- Bleeding

- Cerebral bleeding, bleeding from the surgical incision, injection site or site of intravenous catheter insertion
- Bloody discharge from the site of intravenous catheter insertion
- Bloody cough or sputum
- A decrease in the number of platelets in the blood
- Postoperative decrease in the number of red blood cells
- Severe allergic reaction causing difficulty breathing or dizziness
- Severe allergic reaction causing swelling of the face or throat
- Itchy rash on the skin of red dark bumps caused by an allergic reaction
- A sudden change in the skin affecting its color and appearance
- Itching
- Gastric or intestinal ulcer (including esophageal ulcer)
- Inflammation of the esophagus and stomach
- Reflux of gastric juice into the esophagus
- Abdominal or stomach pain
- Indigestion
- Difficulty swallowing
- Fluid exiting a wound
- Fluid exiting a wound after a surgery.

Side effects of unknown frequency (frequency was not determined yet):

- Difficulty breathing, wheezing
- Decrease in the number or even lack of white blood cells (which help to fight infections)
- Hair loss (alopecia).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not listed in this leaflet, consult your physician.

Reporting side effects
You can report side effects to the Ministry of Health (MoH) by following the link 'Reporting Side Effects of Medication' on the MoH home page (www.health.gov.il) which links to an online form for reporting side effects, or by clicking the link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place out of the reach and sight of children and/or infants. Do not induce vomiting without an explicit instruction from the physician.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- Storage conditions: Store below 25°C in the original package.
- Store in the original packaging to protect from moisture.
- Do not throw away medicines via wastewater. Ask your pharmacist to destroy medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient the capsules also contain the following inactive ingredients:
Acacia, dimeticone, hypromellose, hydroxypropylcellulose, talc, tartaric acid, carrageenan, potassium chloride, titanium dioxide (E171).

What the medicine looks like and what is the content of the package?
White capsules, filled with yellow pellets. The capsule is imprinted in black with the 'Boehringer Ingelheim' logo and 'R75'.
The capsules are packed in blisters of 10, 30 or 60 capsules per pack. Not all the pack sizes may be marketed.

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Boehringer Ingelheim	June 2020

Registration holder: Boehringer Ingelheim Israel Ltd., 89 Medinat Ha'Yehudim St., P.O.B. 4124, Hertzliya Pituach 4676672.
Manufacturer: Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany.

This leaflet was revised in June 2020.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Pradaxa 75: 142-95-32973 00/01/02