SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pradaxa 40 mg coated granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains coated granules with 40 mg dabigatran etexilate (as mesilate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated granules.

Yellowish coated granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from the time the child is able to swallow soft food to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

4.2 Posology and method of administration

Posology

Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food. Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole.

When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.

Dabigatran etexilate coated granules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate coated granules is based on the patient's weight and age as shown in tables 1 and 2. The dose should be adjusted according to weight and age as treatment progresses.

For weight and age combinations not listed in the dosing tables no dosing recommendation can be provided.

Table 1: Single and total daily dabigatran etexilate doses in milligrams (mg) for patients aged less than 12 months. The doses depend on weight in kilograms (kg) and age in <u>months</u> of the patient.

Weight / age combinations		**Single dose in mg**	**Total daily dose in mg**
Weight in kg	**Age in MONTHS**		
2.5 to < 3	4 to < 5	20	40
3 to < 4	3 to < 6	20	40
4 to < 5	1 to < 3	20	40
	3 to < 8	30	60
	8 to < 10	40	80
5 to < 7	0 to < 1	20	40
	1 to < 5	30	60
	5 to < 8	40	80
	8 to < 12	50	100
7 to < 9	3 to < 4	40	80
	4 to < 9	50	100
	9 to < 12	60	120
9 to < 11	5 to < 6	50	100
	6 to < 11	60	120
	11 to < 12	70	140
11 to < 13	8 to < 10	70	140
	10 to < 12	80	160
13 to < 16	10 to < 11	80	160
	11 to < 12	100	200

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

20 mg: One 20 mg sachet
30 mg: One 30 mg sachet
40 mg: One 40 mg sachet
50 mg: One 50 mg sachet
60 mg: Two 30 mg sachets
70 mg: One 30 mg plus one 40 mg sachet
80 mg: Two 40 mg sachets
100 mg: Two 50 mg sachets

Table 2: Single and total daily dabigatran etexilate doses in milligrams (mg) for patients aged 1 year to less than 12 years. The doses depend on weight in kilograms (kg) and age in <u>years</u> of the patient.

Weight / age combinations		Single dose in mg	Total daily dose in mg
Weight in kg	**Age in YEARS**		
5 to < 7	1 to < 2	50	100
7 to < 9	1 to < 2	60	120
	2 to < 4	70	140
9 to < 11	1 to < 1.5	70	140
	1.5 to < 7	80	160
11 to < 13	1 to < 1.5	80	160
	1.5 to < 2.5	100	200
	2.5 to < 9	110	220
13 to < 16	1 to < 1.5	100	200
	1.5 to < 2	110	220
	2 to < 12	140	280
16 to < 21	1 to < 2	110	220
	2 to < 12	140	280
21 to < 26	1.5 to < 2	140	280
	2 to < 12	180	360
26 to < 31	2.5 to < 12	180	360
31 to < 41	2.5 to < 12	220	440
41 to < 51	4 to < 12	260	520
51 to < 61	5 to < 12	300	600
61 to < 71	6 to < 12	300	600
71 to < 81	7 to < 12	300	600
> 81	10 to < 12	300	600

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

50 mg: One 50 mg sachet

60 mg: Two 30 mg sachets

70 mg: One 30 mg plus one 40 mg sachet

80 mg: Two 40 mg sachets

100 mg: Two 50 mg sachets

110 mg: One 110 mg sachet

140 mg: One 30 mg plus one 110 mg sachet

180 mg: One 30 mg plus one 150 mg sachet

220 mg: Two 110 mg sachets

260 mg: One 110 mg plus one 150 mg sachet

300 mg: Two 150 mg sachets

<u>Assessment of renal function prior to and during treatment</u>

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).

Treatment with dabigatran etexilate in paediatric patients with eGFR < 50 mL/min/1.73 m^2 is contraindicated (see section 4.3).

Patients with an eGFR ≥ 50 mL/min/1.73 m^2 should be treated with the dose according to tables 1 and 2.

While on treatment, renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain co-medications, etc).

Duration of use

The duration of therapy should be individualised based on the benefit risk assessment.

Missed dose

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted.
A double dose to make up for missed individual doses must never be taken. If a dose has only been taken partially, there should be no attempt to administer a second dose at that time-point, and the next dose should be taken as scheduled approximately 12 hours later.

Discontinuation of dabigatran etexilate

Dabigatran etexilate treatment should not be discontinued without medical advice. Caregivers should be instructed to contact the treating physician if their treated child develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

Dabigatran etexilate treatment to parenteral anticoagulant:
It is recommended to wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):
Patients should start VKA 3 days before discontinuing dabigatran etexilate.
Because dabigatran etexilate can impact the international normalised ratio (INR), the INR will better reflect VKA's effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to dabigatran etexilate:
The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is < 2.0.

Method of administration

This medicinal product is for oral use.

The coated granules should be mixed with food prior to intake and only be used with apple juice or the soft foods mentioned in the instructions for administration. After mixing with food or apple juice, the medicinal product has to be administered within 30 minutes. The coated granules are not compatible with milk or milk products.

This medicinal product is not compatible with feeding tubes.

Detailed instructions for the use of this medicinal product are provided in 'Instructions for administration' in the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- eGFR < 50 mL/min/1.73 m^2 in paediatric patients
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for 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
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances. These are switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment **(**see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

The efficacy and safety of the specific reversal agent idarucizumab used for adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also section 4.9).

Use of platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non steroidal antiinflammatory drugs (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux increase the risk of GI bleeding.

Risk factors

Table 3 summarises factors which may increase the haemorrhagic risk.

Table 3: Risk factors which may increase the haemorrhagic risk.

	Risk factor
Factors increasing dabigatran plasma levels	Major: • Strong P-gp inhibitors (see section 4.3 and 4.5) • Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5)
Pharmacodynamic interactions (see section 4.5)	• ASA and other platelet aggregation inhibitors such as clopidogrel • NSAIDs • SSRIs or SNRIs • Other medicinal products which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

Precautions and management of the haemorrhagic risk

For the management of bleeding complications, see also section 4.9.

Benefit-risk assessment

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs, see section 4.5), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected benefit outweighs bleeding risks.

Close clinical surveillance

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 3 above). Particular caution should be exercised when dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5).

Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).

Discontinuation of dabigatran etexilate

Patients who develop acute renal failure must discontinue dabigatran etexilate.

When severe bleedings occur, treatment must be discontinued and the source of bleeding investigated. The efficacy and safety of the specific reversal agent (idarucizumab) to dabigatran have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Laboratory coagulation parameters

Although this medicinal product does not in general require routine anticoagulant monitoring, the measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors.
Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but results should be interpreted with caution due to inter-test variability (see section 5.1).
The international normalised ratio (INR) test is unreliable in patients on dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Coagulation test thresholds at trough for paediatric patients that may be associated with an increased risk of bleeding are not known.

Use of fibrinolytic medicinal products for the treatment of acute ischemic stroke

The use of fibrinolytic medicinal products for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the upper limit of normal (ULN) according to the local reference range.

Surgery and interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer (see section 5.2). This should be considered in advance of any procedures. In such cases a coagulation test (see sections 4.4 and 5.1) may help to determine whether haemostasis is still impaired.

Emergency surgery or urgent procedures

Dabigatran etexilate should be temporarily discontinued.

The efficacy and safety of the specific reversal agent (idarucizumab) to dabigatran have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Subacute surgery/interventions

Dabigatran etexilate should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.

Elective surgery

If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery.

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 4.

Table 4: Discontinuation rules before invasive or surgical procedures for paediatric patients

Renal function (eGFR in mL/min/1.73 m^2)	Stop dabigatran before elective surgery
> 80	24 hours before
50 - 80	2 days before
< 50	These patients have not been studied (see section 4.3).

Spinal anaesthesia/epidural anaesthesia/lumbar puncture

Procedures such as spinal anaesthesia may require complete haemostatic function.

The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Postoperative phase

Dabigatran etexilate treatment should be resumed / started after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

Patients at risk for bleeding or patients at risk of overexposure (see table 3) should be treated with caution (see sections 4.4 and 5.1).

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events

There are limited efficacy and safety data for dabigatran etexilate available in these patients and therefore they should be treated with caution.

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of dabigatran etexilate is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section 4.3).

Interaction with P-gp inducers

Concomitant administration of P-gp inducers is expected to result in decreased dabigatran plasma concentrations, and should be avoided (see sections 4.5 and 5.2).

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Active cancer patients

There is limited data on efficacy and safety for paediatric patients with active cancer.

Very specific paediatric population

For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 5) is expected to result in increased dabigatran plasma concentrations.

If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. See also sections 4.3, 4.4 and 5.1).

Table 5: Transporter interactions

P-gp inhibitors
Concomitant use contraindicated (see section 4.3)

Ketoconazole	Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 2.38-fold and 2.35-fold, respectively, after a single oral dose of 400 mg, and by 2.53-fold and 2.49-fold, respectively, after multiple oral dosing of 400 mg ketoconazole once daily.
Dronedarone	When dabigatran etexilate and dronedarone were given at the same time total dabigatran $AUC_{0-\infty}$ and C_{max} values increased by about 2.4-fold and 2.3-fold, respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold, respectively, after a single dose of 400 mg.
Itraconazole, cyclosporine	Based on *in vitro* results a similar effect as with ketoconazole may be expected.
Glecaprevir / pibrentasvir	The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.
Concomitant use not recommended	
Tacrolimus	Tacrolimus has been found *in vitro* to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors.
Cautions to be exercised in case concomitant use (see section 4.4)	
Verapamil	When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see section 4.4). The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of C_{max} by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold and AUC by about 1.5-fold). There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.
Amiodarone	When dabigatran etexilate was co-administered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see section 4.4).
Quinidine	Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1 000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see section 4.4).

Clarithromycin	When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 1.19-fold and C_{max} by about 1.15-fold was observed.
Ticagrelor	When a single dose of 75 mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and C_{max} were increased by 1.73-fold and 1.95-fold, respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold for C_{max} and AUC, respectively. Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by 1.49-fold and 1.65-fold, respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor b.i.d. (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.
Posaconazole	Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when dabigatran etexilate is co-administered with posaconazole.
<u>*P-gp inducers*</u>	
Concomitant use should be avoided.	
e.g. rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, or phenytoin	Concomitant administration is expected to result in decreased dabigatran concentrations. Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total dabigatran peak and total exposure by 65.5 % and 67 %, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.
<u>*Protease inhibitors such as ritonavir*</u>	
Concomitant use not recommended	
e.g. ritonavir and its combinations with other protease inhibitors	These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran etexilate.

P-gp substrate	
Digoxin	In a study performed with 24 healthy subjects, when dabigatran etexilate was co-administered with digoxin, no changes on digoxin and no clinically relevant changes on dabigatran exposure have been observed.

Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with dabigatran etexilate: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfinpyrazone (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section 4.3).

Table 6: Interactions with anticoagulants and antiplatelet aggregation medicinal products

NSAIDs	NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY), NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin.
Clopidogrel	In young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by about 30-40 % (see section 4.4).
ASA	Co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively (see section 4.4).
LMWH	The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin.

Other interactions

Table 7: Other interactions

Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)	
SSRIs, SNRIs	SSRIs and SNRIs increased the risk of bleeding in all treatment groups of a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY).
Substances influencing gastric pH	
Pantoprazole	When Pradaxa was co-administered with pantoprazole, a decrease in the dabigatran AUC of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa.
Ranitidine	Ranitidine administration together with dabigatran etexilate had no clinically relevant effect on the extent of absorption of dabigatran.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with Pradaxa.

Pregnancy

There is limited amount of data from the use of Pradaxa in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pradaxa should not be used during pregnancy unless clearly necessary.

Breast-feeding

There are no clinical data of the effect of dabigatran on infants during breast-feeding.
Breast-feeding should be discontinued during treatment with Pradaxa.

Fertility

No human data available.

In animal studies an effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (representing a 5-fold higher plasma exposure level compared to patients). No other effects on female fertility were observed. There was no influence on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dabigatran etexilate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64 000 patients; thereof approximately 35 000 patients were treated with dabigatran etexilate. The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26 % of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 8 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. They are ranked under headings of System Organ Class (SOC) and frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 8: Adverse reactions

	Frequency
SOC / Preferred term.	treatment of VTE and prevention of recurrent VTE in paediatric patients
Blood and lymphatic system disorders	
Anaemia	Common
Haemoglobin decreased	Uncommon
Thrombocytopenia	Common
Haematocrit decreased	Uncommon
Neutropenia	Uncommon
Agranulocytosis	Not known
Immune system disorder	
Drug hypersensitivity	Uncommon
Rash	Common

Pruritus	Uncommon
Anaphylactic reaction	Not known
Angioedema	Not known
Urticaria	Common
Bronchospasm	Not known
Nervous system disorders	
Intracranial haemorrhage	Uncommon
Vascular disorders	
Haematoma	Common
Haemorrhage	Not known
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Uncommon
Gastrointestinal disorders	
Gastrointestinal haemorrhage	Uncommon
Abdominal pain	Uncommon
Diarrhoea	Common
Dyspepsia	Common
Nausea	Common
Rectal haemorrhage	Uncommon
Haemorrhoidal haemorrhage	Not known
Gastrointestinal ulcer, including oesophageal ulcer	Not known
Gastroesophagitis	Uncommon
Gastroesophageal reflux disease	Common
Vomiting	Common
Dysphagia	Uncommon
Hepatobiliary disorders	
Hepatic function abnormal / Liver function Test abnormal	Not known
Alanine aminotransferase increased	Uncommon
Aspartate aminotransferase increased	Uncommon
Hepatic enzyme increased	Common
Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorder	
Skin haemorrhage	Uncommon
Alopecia	Common
Musculoskeletal and connective tissue disorders	
Haemarthrosis	Not known
Renal and urinary disorders	
Genitourological haemorrhage, including haematuria	Uncommon
General disorders and administration site conditions	
Injection site haemorrhage	Not known
Catheter site haemorrhage	Not known
Injury, poisoning and procedural complications	
Traumatic haemorrhage	Uncommon
Incision site haemorrhage	Not known

Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of dabigatran etexilate may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term dabigatran etexilate treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1 %) had a major bleeding event, 5 patients (1.5 %) a clinically relevant non-major bleeding event and 75 patients (22.9 %) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to < 18 years: 28.6 %) than in the younger age groups (birth to < 2 years: 23.3 %; 2 to < 12 years: 16.2 %). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Dabigatran etexilate doses beyond those recommended, expose the patient to increased risk of bleeding.

In case of an overdose suspicion, coagulation tests can help to determine a bleeding risk (see sections 4.4 and 5.1). A calibrated quantitative dTT test or repetitive dTT measurements allow prediction of the time by when certain dabigatran levels will be reached (see section 5.1), also in case additional measures e.g. dialysis have been initiated.

Excessive anticoagulation may require interruption of dabigatran etexilate treatment. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained.

As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

Management of bleeding complications

In the event of haemorrhagic complications, dabigatran etexilate treatment must be discontinued and the source of bleeding investigated. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber's discretion.

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicinal products have been used. All symptomatic treatment should be given according to the physician's judgement.

Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, direct thrombin inhibitors, ATC code: B01AE07.

Mechanism of action

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

In vivo and *ex vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated quantitative diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations. When the calibrated dTT assay delivers a dabigatran plasma concentration result at or below the limit of quantification, an additional coagulation assay such as TT, ECT or aPTT should be considered.

The ECT can provide a direct measure of the activity of direct thrombin inhibitors.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. Although high aPTT values should be interpreted with caution, a high aPTT value indicates that the patient is anticoagulated.

In general, it can be assumed that these measures of anti-coagulant activity may reflect dabigatran levels and can provide guidance for the assessment of bleeding risk.

Clinical efficacy and safety

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.
In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.
Of the 267 randomised patients, 81 patients (45.8 %) in the dabigatran etexilate group and 38 patients (42.2 %) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1 %) and 7/13 (53.8 %) for patients from birth to < 2 years, 21/43 (48.8 %) and 12/21 (57.1 %) for patients aged 2 to < 12 years, and 47/112 (42.0 %) and 19/56 (33.9 %) for patients aged 12 to < 18 years.
Adjudicated major bleeds were reported for 4 patients (2.3 %) in the dabigatran etexilate group and 2 patients (2.2 %) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6 %) in the dabigatran etexilate arm and 22 patients (24.4 %) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4 %) patients in the dabigatran etexilate group and 3 (3.3 %) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE

in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.
Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4 %) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5 %) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4 %), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4 %), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4 %) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

5.2 Pharmacokinetic properties

Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT / PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to < 2-year-old, 2 to < 12-year-old and 12 to < 18-year-old paediatric VTE patients, respectively.

Experience from adults

Absorption

The absolute bioavailability of dabigatran following oral administration of Pradaxa capsules was approximately 6.5 %.

After oral administration of Pradaxa in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration.
A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anaesthesia, GI paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours. Pradaxa coated granules are not compatible with milk or milk products (see section 4.5).

C_{max} and AUC were dose proportional.

Distribution

In adults, low (34-35 %) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60-70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.

Biotransformation

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction.

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabeled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85 %). Faecal excretion accounted for 6 % of the administered dose. Recovery of the total radioactivity ranged from 88-94 % of the administered dose by 168 hours post dose.
Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

Elimination

Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. Half-life is prolonged if renal function is impaired as shown in table 9.

Special populations

Renal insufficiency
In phase I studies the exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate is approximately 2.7-fold higher in adult volunteers with moderate renal insufficiency (CrCL between 30 and 50 mL/min) than in those without renal insufficiency.

In a small number of adult volunteers with severe renal insufficiency (CrCL 10-30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.3 and 4.4).

Table 9: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function (adults).

glomerular filtration rate (CrCL,) [mL/min]	gMean (gCV %; range) half-life [h]
> 80	13.4 (25.7 %; 11.0-21.6)

> 50-≤ 80	15.3 (42.7 %; 11.7-34.1)
> 30-≤ 50	18.4 (18.5 %; 13.3-23.0)
≤ 30	27.2 (15.3 %; 21.6-35.0)

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomised pharmacokinetic study in non-valvular atrial fibrillation (NVAF) patients with severe renal impairment (defined as creatinine clearance [CrCl] 15-30 mL/min) receiving dabigatran etexilate 75 mg twice daily.
This regimen resulted in a geometric mean trough concentration of 155 ng/mL (gCV of 76.9 %), measured immediately before administration of the next dose and in a geometric mean peak concentration of 202 ng/mL (gCV of 70.6 %) measured two hours after the administration of the last dose.

Clearance of dabigatran by haemodialysis was investigated in 7 patients with end-stage renal disease (ESRD) without atrial fibrillation. Dialysis was conducted with 700 mL/min dialysate flow rate, four hour duration and a blood flow rate of either 200 mL/min or 350-390 mL/min. This resulted in a removal of 50 % to 60 % of dabigatran concentrations, respectively. The amount of substance cleared by dialysis is proportional to the blood flow rate up to a blood flow rate of 300 mL/min. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure.

Hepatic impairment
No change in dabigatran exposure was seen in 12 adult subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls (see section 4.4).

Gender
In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. No dose adjustment is recommended (see section 4.2).

Ethnic origin
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding dabigatran pharmacokinetics and pharmacodynamics.

Pharmacokinetic interactions

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects observed in the repeated dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran.

An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5- to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with

an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

In a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

In lifetime toxicology studies in rats and mice, there was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg.

Dabigatran, the active moiety of dabigatran etexilate mesilate, is persistent in the environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid
Acacia
Hypromellose
Dimeticone 350
Talc
Hydroxypropylcellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

<u>After first opening of the aluminium bag</u>

Once the aluminium bag containing the sachets with the coated granules and the desiccant is opened, the medicinal product must be used within 6 months.

<u>After first opening of the sachet</u>

The opened sachet cannot be stored and must be used immediately after opening.

After preparation

After mixing with soft food or apple juice, the medicinal product has to be administered within 30 minutes.

6.4 Special precautions for storage

The aluminium bag containing the sachets with the coated granules should only be opened immediately prior to use of the first sachet in order to protect from moisture.

After opening of the aluminium bag, the individual sachets should be kept unopened until immediately prior to use in order to protect from moisture.

6.5 Nature and contents of container

Aluminium bag containing 60 silver-coloured PET/Alu/LDPE sachets with the coated granules and one desiccant (labelled “DO NOT EAT” including pictogram and “SILICA GEL”).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
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55216 Ingelheim am Rhein
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 14598/0232

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/11/2021

10 DATE OF REVISION OF THE TEXT

12/04/2024