Summary of product characteristics
Exanta® 24 mg tablets

1. NAME OF THE MEDICINAL PRODUCT
Exanta 24 mg, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 24 mg ximelagatran.
For excipients see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet
Light yellow, elliptical, biconvex tablets marked "AZ" above "E" on one side and "24" on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Prevention of venous thromboembolic events in patients undergoing elective hip or knee replacement surgery.

4.2 Posology and method of administration
The treatment should be initiated after surgery only, with solution for injection (melagatran) and followed by tablets (ximelagatran). Ximelagatran is a prodrug of melagatran.

Solution for injection (melagatran)
A postoperative injection of melagatran 3 mg (0.3 ml) should be administered by subcutaneous injection not earlier than 4 hours and not later than 8 hours after the completion of surgery, provided that adequate haemostasis has been achieved. Timing of the first melagatran injection requires strict adherence. This dose should be continued twice daily during 1 to 2 days until the patient is able to use oral route.

Tablets (ximelagatran)
Treatment with ximelagatran (Exanta 24 mg), one tablet twice daily, can replace the solution for injection from the day after surgery. Tablets can be taken with or without food.

The recommended total duration of treatment is 8 to 11 days. There is currently no data on efficacy and safety of extended prophylaxis beyond 11 days. Therefore the duration of treatment with melagatran followed by ximelagatran should not be prolonged beyond 11 days.

When prolonged anticoagulant therapy is deemed necessary, patients should be switched to therapy where experience in extended prophylaxis exists (see paragraph on switch recommendations between this treatment and other anticoagulants and section 4.5).

Special patients populations

Patients with renal impairment
Exanta 24 mg is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) <30 ml/min) (see section 4.3). In patients with moderate renal impairment (CrCl 30 to 50 ml/min), there is limited clinical experience at the recommended posology. Given the available kinetic data (see section 5.2), Exanta 24 mg should be used with caution and close surveillance is required (see section 4.4).

Elderly
In patients over 75 years of age there is limited clinical experience at the recommended posology. Given the available kinetic data (see section 5.2), Exanta 24 mg should be used with caution and close surveillance is required (see section 4.4).

Patients with hepatic impairment and transaminases abnormalities
The use of Exanta 24 mg is contraindicated in patients with hepatic impairment, and/or with ALAT >2xULN before administration of this treatment. An ALAT value should be obtained before surgery (see section 4.3).

Body weight
There is limited clinical experience with Exanta 24 mg in patients with a body weight <50 kg (see section 4.4).

Clinical experience with Exanta 24 mg in patients with a BMI >35 kg/m^2 is limited and does not allow to rule-out a possible decreased efficacy of this treatment (see section 5.2).

Children and adolescents
Safety and efficacy of Exanta 24 mg in patients aged <18 years have not been studied. This treatment is therefore not recommended for use in children and adolescents.

Switch recommendations between this treatment and other anticoagulants
Heparin/LMWH
- Patients receiving heparin/LMWH *before* administration of melagatran followed by ximelagatran: treatment with melagatran followed by ximelagatran can be started 12 hours after the last heparin/LMWH dose was given.
- Switch to heparin/LMWH *after* administration of melagatran followed by ximelagatran: if prophylactic treatment is to be continued with heparin or LMWH, the first heparin or LMWH injection should be given 12 hours after the last Exanta 24 mg dose.

Vitamin K antagonists
- Patients having a long-term indication for VKA *before* administration of melagatran followed by ximelagatran: as no clinical experience is available and given the potential risk of haemorrhage, patients should be switched to other anticoagulants if uninterrupted anticoagulation is important before surgery.
- Switch to VKA *after* administration of melagatran followed by ximelagatran: as no data on concomitant use of Exanta 24 mg with VKA is available, patients should be switched to heparin/LMWH, which should be continued until appropriate INR control has been achieved with VKA.

4.3 Contraindications

- Known hypersensitivity to melagatran or to ximelagatran or to any of the excipients
- Severe renal impairment (CrCl <30 ml/min)
- Clinically significant active bleeding
- Bleeding or bleeding tendency related to an inherited or acquired coagulation disorder.
- Organic lesion at risk of bleeding
- Hepatic impairment, or a pretreatment ALAT value >2xULN; ALAT value should be obtained before surgery.

4.4 Special warnings and special precautions for use

It is mandatory to follow the recommended dosing regimen and treatment duration. A higher rate of distal deep vein thrombosis (DVT) has been observed with melagatran followed by ximelagatran compared to enoxaparin when the first dose was given between 8 and 12 hours after end of surgery. For distal DVT a possible negative trend was also seen if melagatran followed by ximelagatran was dosed between 4 and 8 hours after end of surgery, but the clinical relevance of this finding is not known (see section 5.1). There is no known antidote to ximelagatran (Exanta 24 mg) (see section 4.9).

The efficacy and safety of melagatran/ximelagatran in hip fracture surgery have not been studied.

A preoperative ALAT value should be obtained before surgery (see section 4.3).

Haemorrhagic risk

The following agents should not be given concomitantly with Exanta 24 mg: vitamin K antagonists, unfractionated heparins and derivatives, LMWHs, fondaparinux, desirudin, thrombolytic agents, GP IIb/IIIa receptor antagonists, clopidogrel, ticlopidine, ASA at doses >500 mg/day, dipyridamole, sulfinpyrazone.

Close clinical surveillance (looking for signs of bleeding and/or anaemia) and measurement of the haemoglobin level is required during and after surgery and throughout the treatment period, especially in the special situations listed below, as they can be expected to increase the bleeding risk:

- Diseases associated with an increased risk of bleeding, such as congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, recent biopsy, recent major trauma, recent intracranial haemorrhage or recent brain, spinal or ophthalmic surgery.
- ASA as antiplatelet drug at doses ≤500 mg/day, NSAIDs and dextran should be used with caution because of the potential increased haemorrhagic risk when administered concomitantly with Exanta 24 mg. If co-administration is essential, close surveillance is required.
- As an increased exposure of melagatran has been observed after oral administration of ximelagatran and erythromycin, there is a potential increased risk of bleeding with concomitant administration (see section 4.5).
- Bacterial endocarditis.

Renal impairment

Melagatran is mainly excreted by the kidney (see section 5.2). Patients with renal impairment exposed to melagatran are at increased risk of bleeding.

Use of ximelagatran is contraindicated in patients with severe renal impairment (CrCl <30 ml/min) (see section 4.3). There is limited clinical experience about the use of ximelagatran at the recommended dose and dosage schedule in patients with moderate renal impairment (CrCl 30 to 50 ml/min). Ximelagatran should be used in caution in these patients and close clinical surveillance (looking for signs of bleeding and/or anaemia) and surveillance of renal function is recommended throughout the treatment period (see section 4.2).

Elderly

There is limited clinical experience about the use of ximelagatran at the recommended dose and dosage schedule in elderly patients. Increasing age is associated with impairment of renal function. Therefore, elderly patients may have reduced elimination and increased exposure to melagatran especially during the post-operative period (see section 5.2). Based on the available pharmacokinetic data, ximelagatran should be used with caution in patients with age >75 years. Close clinical surveillance (looking for signs of bleeding and/or anaemia) and surveillance of renal function are recommended throughout treatment with ximelagatran, especially if there is a history or presence of other risk factors for bleeding (see section 4.2).

Low body weight

There is limited clinical experience about the use of ximelagatran at the recommended dose and dosage schedule in patients with body weight <50 kg. These patients may be at increased risk of bleeding. Exanta 24 mg should be used with caution in these patients (see section 4.2).

Epidural or spinal anaesthesia/spinal puncture

Epidural or spinal haematoma that may result in long-term or permanent paralysis cannot be excluded with concurrent use of melagatran followed by ximelagatran and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with postoperative use of indwelling epidural catheters or the concomitant use of other drugs affecting haemostasis. The risk also appears to be increased by traumatic or repeated puncture. If indwelling catheters are inserted, they should not be removed until at least 8 hours after the latest dose of this treatment.

The next dose of this treatment should not be given earlier than 1 to 2 hours after removal of the indwelling catheter.

Patients should be frequently monitored for signs or symptoms of neurological impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Concomitant use of Exanta 24 mg with agents acting on haemostasis or coagulation may markedly increase the risk of bleeding (see section 4.4). Therefore the following agents should not be administered concomitantly with Exanta 24 mg: vitamin K antagonists, unfractionated heparin and derivatives, LMWHs, fondaparinux, desirudin, thrombolytic agents, GP IIb/IIIa receptor antagonists, clopidogrel, ticlopidine, ASA at doses >500 mg/day, dipyridamole, sulfinpyrazone.

ASA as antiplatelet drug at doses ≤500 mg/day, NSAIDs and dextran should be used with caution because of the potential increased risk of bleeding when administered concomitantly with Exanta 24 mg. If co-administration is essential, close surveillance is required (see section 4.4).

Pharmacokinetic interactions

In vitro drug interaction studies revealed no inhibition of the main cytochrome P450 isoenzymes responsible for the metabolism of many drugs (see section 5.2). These

findings were supported by in vivo studies in healthy volunteers which showed no interaction between treatment with ximelagatran and the following drugs: nifedipine (CYP3A4), diazepam (CYP2C19 and CYP3A4), diclofenac (CYP2C9).

As an increase in AUC (82%) and C_{max} (74%) of melagatran has been observed in a drug interaction study after oral administration of ximelagatran and erythromycin, an increased risk of haemorrhage is possible in case of concomitant use of these medicinal products. The mechanism of this interaction may involve inhibition of transport proteins, possibly P-glycoprotein (P-gp). Therefore, there is a potential for pharmacokinetic interactions with P-gp inhibitors (eg erythromycin, azithromycin, clarithromycin, cyclosporin) possibly leading to an increased exposure of melagatran, and P-gp inducers (eg rifampicin) possibly leading to a decreased exposure of melagatran. Close clinical surveillance (looking for signs of bleeding and/or anaemia) is recommended when these drugs are combined with ximelagatran.

Concomitant use of Exanta 24 mg with vitamin K antagonists, unfractionated heparins and LMWH has not been evaluated.

Switch recommendations between this treatment and other anticoagulants: see section 4.2.

4.6 Pregnancy and lactation

Pregnancy

For ximelagatran no clinical data on exposed pregnancies are available.

Studies in animals have shown reproductive toxicity at dose levels leading to maternal haemorrhage (see section 5.3). The potential risk for humans is unknown. Exanta 24 mg should not be used during pregnancy unless clearly necessary.

Lactation

Melagatran, the active form of ximelagatran, is excreted in breast milk in trace amounts. As a caution, breast-feeding should be stopped during treatment with Exanta 24 mg.

4.7 Effects on ability to drive and use machines

No studies on the effect of Exanta 24 mg on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The adverse events reported in the 1406 patients treated with melagatran followed by ximelagatran in the METHRO III study (see section 5.1) (with a frequency over 2% for events not linked to bleeding), and regardless of their causality link with the treatment, are presented within each system organ class by frequency grouping.

Most of the reported adverse events can be explained by the surgery itself and by the mechanism of action of the drug (see table).

The safety of melagatran followed by ximelagatran, at a daily dose at least equal to the recommended dose, has been evaluated in 4208 patients undergoing major elective orthopaedic surgery of the lower limbs treated for up to 11 days. In studies involving a preoperative dosing regimen the incidence of bleeding events was higher compared to the METHRO III study using a postoperative start. All other adverse events not related to bleeding showed comparable rates across all studies.

An increased incidence of elevated liver enzymes (mainly transaminases) has been reported in long-term use of ximelagatran (over 2 months). These increases were reversible in most patients within approximately 2 months after drug discontinuation.

Class-organ	Frequency	Undesirable event
Blood and lymphatic system disorders	very common (>1/10))	postoperative anaemia
	common (>1/100, <1/10)	bleeding or haematoma at surgical site, gastrointestinal bleeding, urinary bleeding
	uncommon (>1/1000, <1/100)	respiratory bleeding, epistaxis, vaginal bleeding
Injury, poisoning and procedural complications	very common (>1/10)	postoperative seroma
Nervous system disorders	common (>1/100, <1/10)	dizziness, headache
Gastrointestinal system disorders	very common (>1/10)	nausea, vomiting
	common (>1/100, <1/10)	diarrhoea, constipation, dyspepsia, abdominal pain
Renal and urinary disorders	common (>1/100, <1/10)	urinary tract infection
Hepatobiliary disorders	common (>1/100, <1/10)	abnormal liver function tests
Cardiovascular disorders	common (>1/100, <1/10)	hypotension, hypertension, tachycardia, bradycardia
Skin and subcutaneous tissue disorders	common (>1/100, <1/10)	rash, erythematous rash, bullous eruption, pruritus
General disorders	common (>1/100, <1/10)	fever, peripheral oedema, urinary retention, pain, back pain

4.9 Overdose

There is no known antidote for Exanta 24 mg.

Administration of this treatment at doses above the recommended regimen can be expected to result in an increased risk of bleeding. In the event of overdose associated with haemorrhagic complications, treatment should be immediately discontinued and a search made for an underlying cause.

Since melagatran is mainly renally excreted (see section 5.2), satisfactory diuresis should be maintained. The half-life of melagatran after oral administration is short (4–5 hours). Prolongation of APTT indicates remaining anticoagulant effect. Melagatran can be dialysed.

Initiation of appropriate therapy such as surgical haemostasis or blood and/or blood component therapy should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombin inhibitors
ATC code: B01 AE05

Melagatran is a potent, competitive and reversible small molecular direct inhibitor of the serine protease ? -thrombin. This enzyme converts fibrinogen to fibrin in the coagulation cascade; thereby thrombin inhibition prevents thrombus development. Melagatran inhibits both free and fibrin-bound thrombin and thrombin-induced aggregation of platelets.

When administered at the recommended preventive dose, routine coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) are relatively insensitive measures of melagatran activity, and are therefore unsuitable for evaluation of the coagulation status.

An experimental assay, ecarin clotting time (ECT), has been tested. A linear relationship between plasma concentration of melagatran and ECT was shown, but plasma concentrations could not reliably predict an individual patient's risk of bleeding.

In the METHRO III study, efficacy and safety of treatment by melagatran followed by ximelagatran (melagatran 3 mg/0.3 ml administered postoperatively by subcutaneous injection at least 4 hours after completion of surgery and continued twice daily during 1–2 days; then switched to ximelagatran 24 mg tablet twice daily as soon as the patient was able to use oral route) were compared to enoxaparin (40 mg once daily by subcutaneous injection with the first dose administered the day before surgery) for the prevention of thromboembolic events, ie proximal and distal DVT and pulmonary embolism (PE), in 2874 patients (1439 in melagatran followed by ximelagatran group, 1435 in enoxaparin group) aged at least 18 years, undergoing major elective orthopaedic surgery (total hip or knee replacement).

Both treatments were administered for a total duration of 8 to 11 days with no modification of the dosage based on coagulation monitoring.

If the first dose of melagatran was given from the 4th hour after end of surgery (the median timing of the first dose was 8 hours after completion of surgery), the risk of proximal thromboembolic events with melagatran followed by ximelagatran was 5.7% (95% CI 4.3 to 7.1%) versus 6.2% with enoxaparin (95% CI 4.7 to 7.7%), achieving non-inferiority. The risk of total thromboembolic events with melagatran followed by ximelagatran was 31.0 % (95% CI 28.3 to 33.7%) versus 27.3% with enoxaparin (95% CI 24.6 to 29.9%); this difference was not statistically significant (p=0.052). The incidence of symptomatic thromboembolic events during the whole study was similar in the two groups (1.8% and 2.2%, respectively). A higher rate of distal DVT (4.1%; 95% CI 0.8 to 7.5%) was observed with melagatran followed by ximelagatran compared to enoxaparin, but the clinical relevance of this observation is not known. The rate of severe bleeding events was 1.4% (95% CI 0.88 to 2.2%) with melagatran followed by ximelagatran and 1.7% (95% CI 1.05 to 2.47%) with enoxaparin. The rate of heterologous transfusions was statistically significantly lower (p=0.001) in the melagatran followed by ximelagatran group (33.3%; 95% CI 30.8 to 35.8%) than in the enoxaparin group (39.3%; 95% CI 36.7 to 41.9%).

When the first dose of melagatran was given between 4 and 8 hours after the end of surgery, the risk of proximal DVT/PE was 5.6% (611 patients, 95% CI 3.88 to 7.69%) and the risk of total thromboembolic events was 27.2% (613 patients, 95% CI 23.8 to 31.0%), demonstrating non-inferiority relative to enoxaparin for both endpoints. A slightly higher rate of distal DVT (0.5%; 95% CI -3.4 to 4.4%) was observed with melagatran followed by ximelagatran compared to enoxaparin, the clinical relevance of this is not known. A numerically higher rate of severe bleeding events was seen in patients given their first dose of Exanta 4 to 8 hours (1.6%; 95% CI 0.83 to 2.78%) compared to later than 8 hours (1.23%; 95% CI 0.53 to 2.41%) after end of surgery. This slightly higher incidence was not reflected in the need for heterologous transfusions, which was numerically lower if the first dose of melagatran was given between 4 and 8 hours (31.8%; 95% CI 28.5 to 35.2%) compared to more than 8 hours (35%; 95% CI 31.4 to 38.8%) after end of surgery. Independent of timing of the first dose, melagatran followed by ximelagatran was associated with comparable severe bleeding events and a statistically significantly lower need for heterologous transfusions than enoxaparin.

5.2 Pharmacokinetic properties

Ximelagatran is biotransformed to the active form melagatran.

Absorption

After oral administration in patients, ximelagatran is rapidly absorbed and biotransformed to melagatran by de-esterification and reduction. The de-esterification is mediated by esterases while the enzyme mediating the reduction has not been identified, but is not a CYP450 isoenzyme.

The maximum plasma concentration of melagatran is achieved at about 2 hours post dosing. The bioavailability is 23% and is not influenced by food, although food causes a delay of about 1 hour for the absorption of ximelagatran. Steady-state plasma concentrations of melagatran are achieved within 24 hours.

Distribution

The half-life of melagatran after oral dosing with ximelagatran is longer than after dosing with sc melagatran, because of an approximately twofold higher volume of distribution of melagatran (about 30–40 l). This suggests that the more lipophilic ximelagatran is distributed to tissues not accessible for melagatran where biotransformation of ximelagatran to melagatran occurs, which results in a larger volume of distribution of melagatran.

Plasma protein binding for melagatran is low (<15%); therefore interactions with other medicinal products by protein-binding displacement are unlikely.

Metabolism and elimination

Ximelagatran is rapidly biotransformed to melagatran, which is the main active form in plasma.

Two intermediate metabolites are formed. One has a thrombin inhibitory activity similar to melagatran, the other is an inactive compound. These metabolites are present at low concentrations and are rapidly converted to melagatran. The metabolism of ximelagatran occurs in several organs, including liver, lungs, bowels and kidneys.

Melagatran is not further biotransformed and is mainly excreted unchanged in the urine at a rate that corresponds to the glomerular filtration rate. Melagatran exposure after oral dosing with ximelagatran is reproducible and correlates with renal function.

The pharmacokinetics of ximelagatran is not influenced by concomitant intake of alcohol.

In vitro studies revealed no inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4.

The potential for interaction with CYP2B6 and CYP2C8 has not been evaluated.

Special populations

Renal impairment
Melagatran bioavailability after oral dosing with ximelagatran is higher in patients with renal impairment (21.5%) than in subjects without renal impairment (15.8%). There is a linear relationship between renal function and melagatran clearance. For patients with severe renal impairment (CrCl <30 ml/min), exposure (AUC) to ximelagatran (administered orally) is increased about sixfold (fourfold with melagatran subcutaneous) and the half-life is increased about threefold compared to the subjects without renal impairment (see sections 4.2 and 4.3).

Elderly
Specific pharmacokinetic studies in elderly have been carried out with single dosing of melagatran or ximelagatran in a total of 24 subjects aged 56 to 71 years. They showed a 50% to 60% increase in AUC and a more than 20% increase in C_{max} in patients aged 56 to 71 years compared to young subjects.

Melagatran kinetics was assessed in population kinetic studies after repeated dosing in older patients (up to 90 years) with CrCl >30 ml/min. The decrease in melagatran clearance was correlated to the decrease in creatinine clearance.

Hepatic impairment
The exposure of melagatran was not significantly modified in 12 subjects with moderate hepatic impairment after oral administration of ximelagatran as compared to 12 control subjects after adjustment for CrCl.

Obese subject
After oral administration of ximelagatran, there were no significant differences in the pharmacokinetics of melagatran between obese (BMI 32 to 39 kg/m^2) and non-obese subjects, except a decrease of AUC linked to an increase of CrCl.

Gender
After adjustment for weight, no influence of gender on the pharmacokinetics of melagatran was observed.

Ethnic origin
No influence of ethnic origin on the pharmacokinetics of ximelagatran was observed.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In pregnant rats ximelagatran caused a slight increase in fetal malformations which was not dose-related and occurred in the presence of maternal toxicity (haemorrhage). In pregnant rabbits ximelagatran caused a dose-related decrease in litter size and an increase in pre- and postimplantation losses, abortions and fetal abnormalities which were associated with maternal toxicity (haemorrhage) (see section 4.6).

Melagatran tested positive in a guinea-pig model of allergic contact dermatitis.

A transient allergic-like reaction upon standard vaccination was observed in dogs treated with oral melagatran. A direct relation to melagatran treatment is uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- cellulose microcrystalline
- mannitol
- povidone K90
- sodium starch glycolate (type A)
- sodium stearyl fumarate

Film-coating :
- hypromellose
- iron oxide yellow (E172),
- macrogols 6000
- titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
3 years.

6.4 Special precautions for storage
No special precautions for storage.

6.5 Nature and contents of container
Blisters of PVC/PVDC/Aluminium of 10, 10x1 (single dose unit), 14, 20, 20x1 (single dose unit), 28, 30, 30x1 (single dose unit), 50, 50x1 (single dose unit), 56, 60, 60x1 (single dose unit), 70x1 (single dose unit), 90x1 (single dose unit), 98 and 100, 100x1 (single dose unit) tablets and HDPE bottles of 60, 100 and 500 tablets with PP caps. Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal
No special requirements.