XIMELAGATRAN: A NEW DIRECT THROMBIN INHIBITOR
Mehta Hiren R\(^1\)*, Patel Paresh B\(^2\), Galani Varsha J\(^3\), Patel Kinjal B\(^3\)

\(^1\)Torrent Research Centre, Near Bhat village, Gandhinagar, Gujarat, India  
\(^2\)A R Collage of Pharmacy, Vallabhidhyanagar, Anand, Gujarat, India  
\(^3\)K. B. Institute of Pharmaceutical Education and Research Centre, Gandhinagar, Gujarat, India

Article Received on:15/02/2011 Revised on:26/03/2011 Approved for publication:15/04/2011

*Hiren Mehta, Torrent Research Centre, Near Bhat village, Gandhinagar-382424, Gujarat, India  
E-mail: hirenpharm@rediffmail.com

ABSTRACT
Venous thromboembolism is a serious illness that affects patient morbidity and mortality and presents a significant management challenge to healthcare providers worldwide. Despite major achievements in the significant reduction of thromboembolic complications, the most common therapies currently used for prevention and treatment of venous thromboembolism – heparins and vitamin K antagonists such as warfarin – have several limitations. Warfarin sodium is an effective oral anticoagulant drug. However, warfarin has a narrow therapeutic window with significant risks of hemorrhage at therapeutic concentrations. Dosing is difficult and requires frequent monitoring. New oral anticoagulant agents are required to improve current anticoagulant therapy. Furthermore, while warfarin is effective in venous disease, it does not provide more than 60% risk reduction compared with placebo in venous thrombosis prophylaxis and considerably lower risk reduction in terms of arterial thrombosis. Unlike warfarin and heparin, these direct thrombin inhibitors are able to inhibit fibrin-bound thrombin and so produce more effective inhibition of coagulation. Importantly, some members of this class of drugs have been developed for oral administration. Ximelagatran is an oral pro-drug of melagatran, a synthetic small peptidomimetic with direct thrombin inhibitory actions and anticoagulant activity. As an oral agent, ximelagatran has a number of desirable properties including a rapid onset of action, fixed dosing, stable absorption, apparent low potential for medication interactions, and no requirement for monitoring of drug levels or dose adjustment. It has a short plasma elimination half-life of about 4 hours in cases of unexpected hemorrhage or need for reversal.

KEY WORDS: Thromboembolism, Anticoagulants, Direct thrombin inhibitors, Ximelagatran.

INTRODUCTION
Oral anticoagulants have been used in clinical practice for more than 60 years. The most commonly prescribed oral anticoagulant has been warfarin sodium (either Coumadin® or Marevan®) or longer-acting coumarin preparations or indanedione derivatives. Warfarin is an effective anticoagulant, but has a narrow therapeutic window with significant risks of hemorrhage at therapeutic drug concentrations.\(^1\)

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is a serious and potentially fatal condition that places a significant economic burden on healthcare providers. Its annual incidence is approximately 1 in 1000 individuals per year, but this is likely to be an underestimate, because the condition is often asymptomatic, with the first clinical sign being pulmonary embolism, which can be fatal.\(^2\)

The risk of developing venous thromboembolism increases with age, prolonged immobility and major surgery. Therefore, venous thromboembolism is a particular problem in elderly patients undergoing major orthopaedic surgery.\(^2,3\) Numerous clinical trials have demonstrated that the provision of anticoagulant therapy (oral vitamin K antagonists, parenteral unfractionated heparin [UFH], low molecular- weight heparin [LMWH], or the factor Xa inhibitor fondaparinux) dramatically reduces the postoperative morbidity associated with orthopaedic surgery.\(^3\) The vitamin K antagonists such as warfarin have remained the only oral anticoagulants available since their introduction in 1942. Although effective and widely used for a broad range of indications, they have serious limitations. Close monitoring to maintain the international normalized ratio (INR) within a desired range is required to maintain effectiveness and minimize bleeding complications because of the narrow therapeutic range. Also, they have a slow onset of action so therapy must be initiated with a parenteral anticoagulant when a rapid effect is needed. Vitamin K antagonists also have prolonged action after stopping, which creates difficulties in managing bleeding complications or when treatment must be interrupted for invasive procedures. Dosing is complicated by numerous
interactions with food and drugs, and marked biological variations in response between patients.\(^4\)

Venous thrombi occur as a result of inappropriate plasma coagulation in patients with hypercoagulability or with venous trauma or stasis. Coagulation is dependent on a highly regulated cascade of proteolytic enzymes and co-factors that ultimately leads to the production of an insoluble fibrin network.\(^2\) Two coagulation pathways exist: the intrinsic pathway, which is activated when blood comes into contact with negatively charged surfaces, and the extrinsic pathway, which is activated by the exposure of tissue factor at sites of vascular injury. Both these pathways are linked and converge after the activation of factor X, which then cleaves prothrombin (factor II) to produce thrombin, the final protease in the coagulation cascade. Thrombin cleaves fibrinopeptides A and B from fibrinogen to yield soluble fibrin, which is cross-linked to form insoluble fibrin and a more stable coagulum.\(^2,4\) However, it also has an important effect in feedback amplification of coagulation, as small amounts of thrombin proteolytically activate Factors V and VIII, and this greatly increases their cofactor activities. Thrombin also converts Factor XI to Factor XIa, which activates Factor XIII; this stabilizes fibrin by isopeptide cross-linking. Another important hemostatic effect is proteolytic activation of thrombin-activatable fibrinolysis inhibitor, which inhibits fibrinolysis by cleaving N-terminal lysines from fibrin to limit plasminogen binding. Additionally, thrombin is a potent platelet activator, and it has effects on a variety of vascular cells through activation of specific receptors. Thrombin also has an important anticoagulant effect after binding to the endothelial receptor, thrombomodulin, which enables it to convert Protein C to activated Protein C; this inactivates Factors Va and VIIIa. Therefore, thrombin inhibition may result in a variety of effects including inhibition of coagulation, platelet activation and fibrinolysis. However, it could potentially have a procoagulant effect under some circumstances through reduced formation of activated Protein C, and it may influence vascular responses to injury through blocking cellular effects.\(^2,4\)

As discussed earlier, there are several drawbacks to the clinical use of current anticoagulant treatments. In particular, the unpredictable pharmacokinetics of warfarin and heparin and the associated risk of bleeding or under treatment necessitate routine coagulation monitoring. There is, therefore, a clinical need for alternative anticoagulation therapies. Among other properties, the ideal anticoagulant should have a predictable pharmacokinetic profile such that coagulation monitoring is not required. In addition, oral availability is important if new drugs are to be useful as alternatives to warfarin for long-term, outpatient treatment.\(^5\)

Thrombin is a particularly attractive target for anticoagulation therapies because of the central part that it plays in the coagulation cascade. Molecules that directly inhibit thrombin have some theoretical advantages over current anticoagulants. For example, neither heparins nor other indirect coagulation inhibitors are active against fibrin bound thrombin. This is important, because fibrin-bound thrombin remains active and promotes continued thrombus growth. Heparin is able to link thrombin to fibrin and so blocks the heparin-binding site on thrombin that is necessary for its interaction with heparin activated antithrombin. Direct thrombin inhibitors, however, have the potential to inhibit fibrin-bound thrombin, as no steric hindrance is present. In addition, direct thrombin inhibitors do not bind to platelet factor 4 (as do heparins) and so do not cause heparin-induced thrombocytopenia.\(^2\) Some other advantages of direct thrombin inhibitors having anticoagulants with improved pharmacological properties, such as suitability for oral administration, a rapid onset of action, and no requirement of anticoagulation monitoring and dose adjustment.\(^3\)

**INTRODUCTION TO XIMELAGATRAN**

Ximelagatran (Exanta\(^\text{TM}\), AstraZeneca) is the first oral direct thrombin inhibitor in advanced clinical development. Based on its promising pharmacological properties, ximelagatran has been the subject of an extensive clinical trial programme, examining its efficacy and safety in several clinical areas for the prevention and treatment of thromboembolic disorders. The clinical trials of ximelagatran for the prevention of VTE following major orthopaedic surgery, in which approximately 60% to 70% of patients received neuraxial anaesthesia has been, investigated both pre-operative and postoperative commencement of anticoagulant dosing. There have been no reports of spinal or epidural haematomas.\(^3\)

Ximelagatran is orally active direct thrombin inhibitors. It belongs to ethyl N-[(R)-cyclohexyl-[[2S]-2-[[4-(hydroxycarbamimidoyl) benzyl]carbamoyl]-1-zetidinyl] carbonyl[methyl] glycin (mehta Hiren R et al. IRJP 2 (4) 2011 9-15). Its having molecular formula C\(_{23}\)H\(_{35}\)N\(_{2}\)O\(_{5}\) and having molecular weight 474 and 429 after conversion into the active metabolite megalatran.\(^6\)

**MECHANISM OF ACTION**

After oral administration, ximelagatran is rapidly absorbed and is extensively metabolized to its active form of melagatran via hydrolysis and reduction. Melagatran is a competitive, direct, and reversible inhibitor of clot-bound and free thrombin, which
prevents the conversion of fibrinogen to fibrin, thereby inhibiting coagulation (see figure 1).7

PHARMACODYNAMICS
Ximelagatran is an oral prodrug derivative of melagatran, a low-molecular-weight potent direct thrombin inhibitor.8 Development of the novel, derivatized prodrug approach was essential because melagatran and other active direct thrombin inhibitors exhibit poor intestinal absorption.9 Ximelagatran undergoes rapid enzymatic conversion to melagatran via 2 intermediates, ethyl-melagatran (from the ethyl ester of melagatran formed by reduction of the hydroxyl group) and hydroxy-melagatran (the hydroxyamidine of melagatran, formed by hydrolysis of the ethyl group) (see Figure 2). This conversion in vivo probably occurs in several tissues. Enzymatic conversion in vitro occurs in microsomal preparations from the liver, intestinal membrane, and kidney. The highest activity was found in liver mitochondria. Cytochrome P450 (CYP) enzymes are unlikely to be involved in the bioconversion of ximelagatran as no reduction of hydroxylmelagatran was found in preparations of 9 different CYP isoenzymes. The conversion of the intermediates to melagatran occurs rapidly in all ethnic groups including African, Asian, and Caucasian. Hydroxyl-melagatran, as with ximelagatran, is an ineffective thrombin inhibitor (potency ~1% of melagatran) while ethyl-melagatran’s anticoagulant activity is the same as melagatran.1

PHARMACOKINETICS
Ximelagatran is an orally active direct thrombin inhibitor. After oral administration, Ximelagatran rapidly converted into its active form melagatran, a potent inhibitor of thrombin that prevents both thrombin activity and generation.10 Its oral availability is 18% to 25% in its active form, reaching a peak concentration in 1.5 to 2.5 hours. It is only about 15% protein bound, and its half-life is about three hours in healthy patients.1,2,8,9 However, following oral administration, ximelagatran is rapidly and nearly completely absorbed with a Cmax of 0.33 hours, and food has little effect on absorption. Ximelagatran is metabolized rapidly with a half-life of unmetabolized ximelagatran of 0.34 hours, and approximately 20% is converted to melagatran with a low interindividual variability in the area under the curve of approximately 20%. Other metabolites include ethylmelagatran and OH-melagatran that form in small amounts and are eliminated rapidly. The tmax of melagatran following oral ximelagatran is approximately 2 hours.1,2,4 Melagatran is primarily excreted in the kidneys (80%), and its half-life is thus prolonged in patients with renal dysfunction.8

Unlike warfarin and other vitamin K antagonists, ximelagatran has a very wide therapeutic interval that enables it to be administered safely across a wide range of doses without an increased risk of bleeding. It has a predictable and stable pharmacokinetic profile and is unaffected by patient body weight, age, sex, or ethnic origin.1 The metabolism of melagatran is independent of the hepatic cytochrome P450 system, leading to a low potential for drug interactions. Unlike warfarin, ximelagatran has no known food interactions and does not require coagulation monitoring or dose adjustment. Recent studies have also demonstrated that the pharmacokinetics and pharmacodynamics of oral ximelagatran are unaffected by alcohol or aspirin.7

Pharmacokinetic Study
One study was conducted in healthy volunteers to check the effect of different antibiotics on the pharmacokinetic and pharmacodynamic of the melagatran. To check the effects of amoxicillin, doxycycline, ciprofloxacin, azithromycin, and cefuroxime on the pharmacokinetics and pharmacodynamics of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran, which is a substrate for the P-glycoprotein pump (Pgp) transporter but is not metabolized by the cytochrome P450 (CYP450) enzyme system? Author included total five parallel groups of 16 healthy volunteers received two sequential treatments. The first treatment was a single 36-mg dose of ximelagatran. During the second treatment period, one of the above antibiotics was given on days 1–5 after a washout of at least 2 days. A single 36-mg oral dose of ximelagatran was given on the mornings of days 1 and 5 of the second treatment period. There was no pharmacokinetic interactions were detected between ximelagatran and amoxicillin, doxycycline, or ciprofloxacin as the least-squares geometric mean treatment ratio of ximelagatran with-to-without antibiotic fell within the intervals of 0.80–1.25 for the area under the curve (AUC) and 0.7–1.43 for Cmax. After co-administration with azithromycin, the least square mean ratio with-to-without antibiotic for AUC of melagatran was 1.60 (90% CI, 1.40–1.82) on day 1 and 1.41 (90% CI, 1.24–1.61) on day 5. For melagatran Cmax, the corresponding ratios were 1.63 (90% CI, 1.38–1.92) and 1.40 (90% CI, 1.18–1.66). After coadministration with cefuroxime, the ratios were 1.23 (90% CI, 1.07–1.42) and 1.16 (90% CI, 0.972–1.38) for AUC and 1.33 (90% CI, 1.07–1.66) and 1.19 (90%CI, 0.888–1.58) for Cmax of melagatran. Co-administration with the antibiotics did not change mean time to Cmax, half-life, or renal clearance of melagatran. The melagatran plasma concentration-response relationship for activated partial thromboplastin time (APTT) prolongation was not
altered by any of the studied antibiotics, but the increased plasma concentrations of melagatran after co-administration of ximelagatran with azithromycin resulted in a minor increase in the mean maximum APTT of about 15%.  

Authors concluded that the pharmacokinetics of ximelagatran was not affected by amoxicillin, doxycycline, or ciprofloxacin. Melagatran exposure was increased when ximelagatran was co-administered with azithromycin and, to a lesser extent, with cefuroxime. APTT was not significantly altered by any of the antibiotics.  

In another study was also conducted for dose-optimization, study18 was conducted to determine the superiority and safety of ximelagatran, at doses of 24 mg or 36 mg twice daily, compared with warfarin. That study showed a significant reduction in the prevalence of deep-vein thrombosis, pulmonary embolism, and/or death with no increase in major bleeding with a dose of 36 mg of ximelagatran twice daily compared with adjusted-dose warfarin (p = 0.003).  

CLINICAL TRIALS

The METHRO Trial

The METHRO I (Melagatran as prophylaxis of thrombosis in orthopaedic surgery), a dose-ranging pilot study, and METHRO II, a phase II study, have found an overall dose-dependent decrease in venographic total and proximal DVT and/or symptomatic PE with increasing doses of ximelagatran–melagatran. The METHRO III study compared the use of ximelagatran–melagatran with enoxaparin in a randomized study of 2788 patients undergoing major orthopedic surgery. Doses of enoxaparin were 40 mg once daily commencing 12 hours preoperatively then daily for 1–10 days compared with melagatran 3 mg subcutaneously 4–12 hours postoperatively, then ximelagatran 24 mg orally twice daily commencing on day 1 or 2 postoperatively. Over all conclude that the venous thromboembolism occurred in 355/1146 (31.0%) and 306/1122 (27.3%) patients in the ximelagatran and enoxaparin group, respectively, so a difference in risk of 3.7% in favour of enoxaparin (p = 0.053). Bleeding was comparable between the two groups.  

The EXPRESS Trial

The Extended Prophylaxis Evaluation Surgery Study (EXPRESS), a randomized, double-blind, parallel group, placebo controlled trial, consisted of two treatment arms. The study was conducted to evaluate the safety and efficacy of ximelagatran, compared with enoxaparin (Lovenox®, Aventis), in preventing VTE after total hip and knee replacement surgery. Patients in one arm of the trial received melagatran 2 mg subcutaneously immediately before surgery and then 3 mg subcutaneously the night after surgery (n = 1,377). The patients continued therapy with oral ximelagatran 24 mg twice daily. Patients in the second arm received enoxaparin 40 mg subcutaneously once daily starting the night before surgery (n = 1,387). Treatment of patients in both arms continued for eight to 11 days. The rate of deep vein thrombosis (DVT) and pulmonary embolism (PE). The overall rate of DVT and PE in the ximelagatran patients (2.3%) was lower than that in the enoxaparin group (6.3%). The total rate of VTE was lower in the ximelagatran arm (20.3%) than in the enoxaparin arm (26.6%). It is interesting that no differences in clinically significant bleeding were reported among the two groups. However, bleeding events were higher in the patients in the ximelagatran arm (3.3%) than those in the enoxaparin arm (1.2%). The authors of the study concluded that subcutaneous melagatran, in combination with oral ximelagatran, was more effective in preventing VTE than enoxaparin alone in patients with total hip or total knee replacement surgery.  

The EXULT Trial

The Exanta Used to Lessen Thrombosis (EXULT) study was a multicenter, randomized, double-blind trial consisting of three treatment arms. A total of 2,301 patients underwent total knee replacement surgery. In one group, ximelagatran 24 mg was given twice daily; the patients in the second arm received ximelagatran 36 mg twice daily. Both dosages were initiated on the morning after surgery. A third study arm consisted of patients who received warfarin, initiated during the evening of the day of surgery. The doses in the warfarin arm were titrated to a goal International Normalized Ratio (INR) of 2 to 3. All treatments in each study arm were continued for seven to 12 days. The study endpoints evaluated the incidence of VTE, all causes of mortality, and bleeding. Combined incidences of DVT and PE with all causes of mortality showed that ximelagatran 36 mg twice daily (20.3%) was more effective than warfarin (27.6%). No differences were reported between endpoints that were independently assessed among the three study arms. Bleeding was evaluated, and no major differences were reported among the groups. The bleeding incidence was noted to be associated with the dosage: ximelagatran 24 mg (4.8%), ximelagatran 36 mg (5.3%), and warfarin (4.5%). In conclusion, ximelagatran showed superior effects over traditional warfarin therapy in preventing VTE after total knee replacement.
Liver enzyme concentrations were elevated within the first six months of therapy and decreased with or without drug discontinuation. Long-term safety over 35 days and liver enzyme levels were also evaluated. Liver enzymes of ALT were more than three times the ULN with ximelagatran in contrast to comparator agents with more than twice the ULN of bilirubin. Of nine patients who died, three were in the ximelagatran group. 

**ADVERSE EFFECTS**

The most common and expected adverse drug event (ADE) associated with ximelagatran is bleeding. Clinical trials have shown that the risk of bleeding associated with ximelagatran is comparable to that of traditional anticoagulants. However, the incidence is reported to be less than with other conventional therapies. Elevations of liver enzymes have also been noted in clinical trials. Within the first two to six months of treatment with ximelagatran, up to 6% of patients had elevated serum ALT levels as high as three times the ULN. However, these levels returned to normal in most of the patients whether or not they continued therapy. Because of the uncertainty of the significance of liver enzyme elevations, authorities have recommended that liver function tests, in particular ALT testing, be performed before the initiation of ximelagatran and every two months thereafter for at least the first six months, then periodically. Recommendations have been implemented to monitor patients clinically, and patients are urged to adhere to protocols in order to prevent possible ADEs.

**CONTRAINDICATION**

Ximelagatran is contraindicated in patients with a history of hypersensitivity to ximelagatran, melagatran, or any of its components. The use of ximelagatran is prohibited in patients with any type of severe, active bleeding.

**TOLERABILITY**

Aside from hemorrhage, ximelagatran–melagatran has been remarkably free of significant adverse toxicities. Most concern has been placed on the dose-dependent increase in liver enzymes, predominantly elevated ALT, which is usually unaccompanied by clinical sequelae. This has been found in 6%–12% of patients in clinical studies with the biochemical abnormality typically occurring in 1–6 months of therapy, rarely developing after 6 months of treatment. In all clinical studies, patients required monthly screening of liver biochemistry in the first 6 months. The study medication was ceased if ALT exceeded 5 times ULN at any time. If ALT was 3–5 times ULN, more frequent monitoring was performed with 6% of patients overall of increased ALT to >3 times ULN. Only about one-half of patients discontinued the study as a result of this. With time, the ALT tends to

**The THRIVE III Trial**

The Oral Direct Thrombin Inhibitor, ximelagatran, for Venous Thromboembolism (THRIVE) study, a multicenter, double-blind trial, included 1,233 patients with documented DVT and PE and appropriate anticoagulation therapy for six months’ duration. This study evaluated the efficacy and safety of ximelagatran in preventing secondary events associated with VTE. Inclusion criteria were based on the receipt of either placebo or ximelagatran 24 mg twice daily for 18 months after the initial six month anticoagulation period. The primary endpoint was the evaluation of any recurrences of VTE. Patients receiving ximelagatran experienced a significantly lower incidence of VTE recurrence than did patients receiving placebo. Bleeding, described as a major hemorrhage, was not significant between study groups. Overall, ximelagatran was safe and effective in preventing the secondary events of VTE.

**The SPORTIF III and V Trials**

The Stroke Prevention by Oral Thrombin Inhibitor in Atrial Fibrillation III (SPORTIF III) study was a randomized, open-label, parallel-group trial with blinded event assessment. The trial included 3,407 patients at 259 study centers in 23 countries. SPORTIF V was also a randomized, open-label, parallel-group trial with a similar design in utilizing double-blind treatment investigation. This trial involved 3,922 patients in 409 North American study centers. For both studies, the primary endpoint was the incidence of all strokes and systemic embolic events among the ximelagatran and warfarin treatment groups. Secondary endpoints included stroke, embolism, myocardial infarction, ischemic stroke, transient ischemic attack (TIA), bleeding, treatment discontinuation, and death. In an intent-to-treat analysis of SPORTIF III, 3,407 patients received ximelagatran 36 mg twice daily and 1,703 received warfarin with an INR of 2–3. A mean follow-up period of 17.4 months demonstrated 40 documented cases of increased risk of stroke and systemic embolism with ximelagatran and 56 cases of increased risk with warfarin. The data confirmed the non-inferiority of ximelagatran over warfarin. In SPORTIF V, patients were followed for a mean of 20 months. The data from this trial also verified the non-inferiority of ximelagatran over warfarin. Bleeding was observed in both treatment groups, and the incidence was higher in the ximelagatran group. Patients receiving ximelagatran demonstrated an increase in alanine aminotransferase (ALT) levels greater than three times the upper limits of normal (ULN) at 6% compared with the warfarin patients at 0.7–0.8%.
decrease whether or not the drug is discontinued although a small percentage (data unpublished) still has persistent elevation. However, a small percentage of patients became jaundiced (0.4% in the ESTEEM study) or developed symptoms possibly attributable to liver dysfunction. In the METHRO III study, 2 patients suffered MI during the treatment period and 1 succumbed to cardiogenic shock in the follow up period. No such event occurred in the control arm. Cardiomyopathy, ischemic heart disease, and congestive heart failure were causes of 3 deaths in the ximelagatran group in the METHRO II studies. No comments were made by the authors as to potential reasons for these adverse events or their significance. Similar findings regarding MI were not observed in the other clinical studies of ximelagatran. 

CONCLUSION

Venous thromboembolism is a serious condition that requires effective and safe anticoagulation therapy. The current modalities for its prevention and treatment have many limitations, particularly relating to unpredictable pharmacokinetics and pharmacodynamics. Thrombin is a key enzyme in the coagulation cascade and as such is an attractive target for novel anticoagulant therapies. A new class of drugs has been developed that produces direct inhibition of thrombin. Ximelagatran—the first oral direct thrombin inhibitor, is at the most advanced stage of development and its efficacy and safety in venous thromboembolism have been demonstrated in clinical trials. It has a reproducible pharmacokinetic and pharmacodynamic profile, and thus fixed doses can be administered without the need for coagulation monitoring. The characteristics of ximelagatran have led to its investigation in the prevention of venous thromboembolism in patients undergoing major elective orthopaedic surgery, the treatment and long-term secondary prevention of venous thromboembolism, prevention of stroke in patients with atrial fibrillation and prevention of major cardiovascular events after acute myocardial infarction. The new class of direct thrombin inhibitors, particularly orally available, has the potential to achieve considerable improvement in the prevention and treatment of venous thromboembolism.

REFERENCES

Figure 1: Mechanism of Action of Ximelagatran

Figure 2: Chemical Structure of Ximelagatran and Melagatran