ינואר 2018

הנדון: עדכון עלון לרופא לתכשיר Praxbind
(idarucizumab 50 mg/ml)

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת בורינגר אינגלהיים מבקשת לעדכן על עדכון העלון לרופא בינואר 2018 כמפורט בהמשך.

ההתוויות המאושרות לפי משרד הבריאות הישראלי:

Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding.

העדכונים הבאים נוספו/נמחקו מעלוני התכשיר. טקסט בצבע אדום מהווה תוספת מידע, טקסט מודגש הינו החמרה, טקסט עם קו חוצה מהווה מחיקה מגוף העלון. רק העדכונים המשמעותיים מוצגים בעדכון זה.

בברכה,

חברת בורינגר אינגלהיים ישראל

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עדכונים בעלון לרופא:

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.~~None.~~

4.8 Undesirable effects

In a phase III trial t~~T~~he safety of Praxbind has been evaluated in 503 patients, who had uncontrolled bleeding or required emergency surgery or procedures and were under treatment with Pradaxa (dabigatran etexilate), as well as in 224 ~~healthy subjects as well as 123~~ volunteers in phase I trials. ~~patients in an ongoing phase III trial, who had uncontrolled bleeding or required emergency surgery or procedures and were under treatment with dabigatran etexilate.~~

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical efficacy and safety

Three randomised, double-blind, placebo-controlled Phase I studies in 283 subjects (224 treated with idarucizumab) were conducted to assess the safety, efficacy, tolerability, pharmacokinetics and pharmacodynamics of idarucizumab, given alone or after administration of dabigatran etexilate. The investigated population consisted of healthy subjects and subjects exhibiting specific population characteristics covering age, body weight, race, sex and renal impairment. In these studies the doses of idarucizumab ranged from 20 mg to 8 g and the infusion times ranged from 5 minutes to 1 hour.

Representative values for pharmacokinetic and pharmacodynamics parameters were established on the basis of healthy subjects aged 45-64 years receiving 5 g idarucizumab (see sections 5.1 and 5.2).

~~A~~ One prospective, open-label, non-randomized, uncontrolled study (RE-VERSE AD) was conducted ~~is currently ongoing~~ to investigate the treatment of adult patients who presented with dabigatran-related life-threatening or uncontrolled bleeding (Group A) or who required emergency surgery or urgent procedures (Group B). The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, based on central laboratory determination of dilute thrombin time (dTT) or ecarin clotting time (ECT). A key secondary endpoint ~~is~~ was the restoration of haemostasis.

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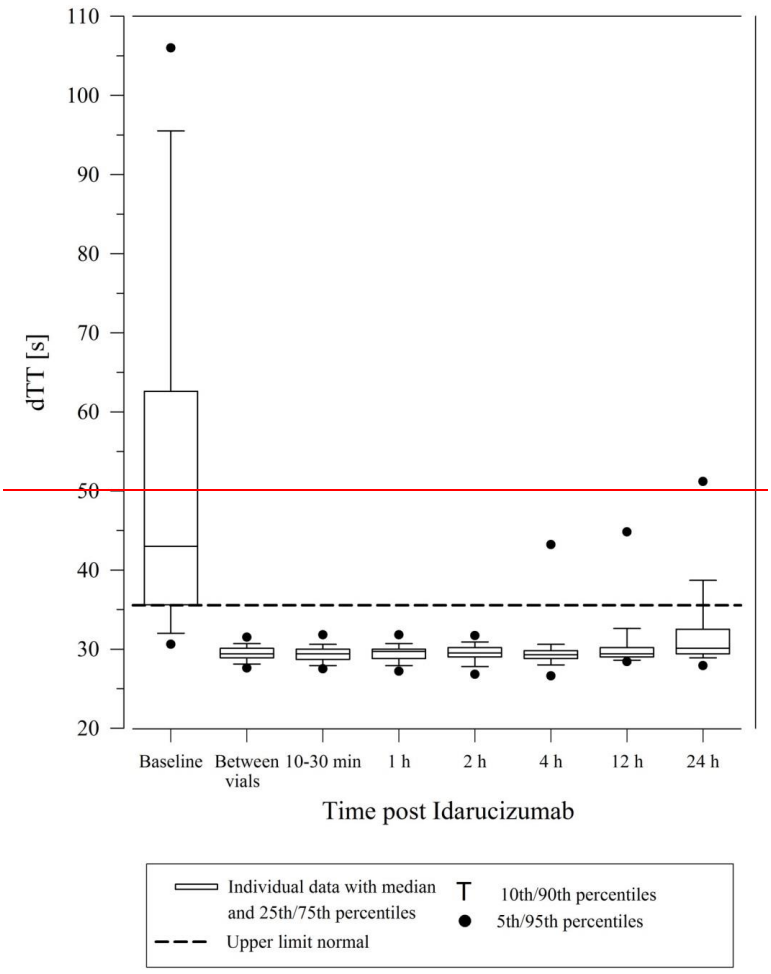
~~An interim analysis of~~ RE-VERSE AD included data for ~~123~~ 503 patients: ~~66~~ 301 patients with serious bleeding (Group A) and ~~57~~ 202 patients requiring an urgent procedure/surgery (Group B). Approximately half of the patients in each group were male. The median age was ~~77~~ 78 years and the median creatinine clearance was ~~61~~ 52.6 mL/min. ~~Approximately 68~~61.5% of patients in Group A and ~~63~~62.4% of patients in Group B had been treated with dabigatran 110 mg twice daily. ~~Results of central laboratory evaluations were available for a subset of 90 patients (51 in Group A, 39 in Group B).~~

Reversal was only evaluable for those patients showing prolonged coagulation times prior to idarucizumab treatment. Most patients ~~(>89%),~~ in both Groups A and B, achieved complete reversal of the anticoagulant effect of dabigatran ~~as measured by~~ (dTT: 98.7%; ECT: 82.2%; aPTT: 92.5% of evaluable patients, respectively) ~~or ECT~~ in the first 4 hours after administration of 5 g idarucizumab. Reversal effects were evident immediately after administration.

Figure 1 – Reversal of dabigatran-induced clotting time prolongation determined by dTT in ~~90~~ patients from the RE-VERSE AD study (N=487)



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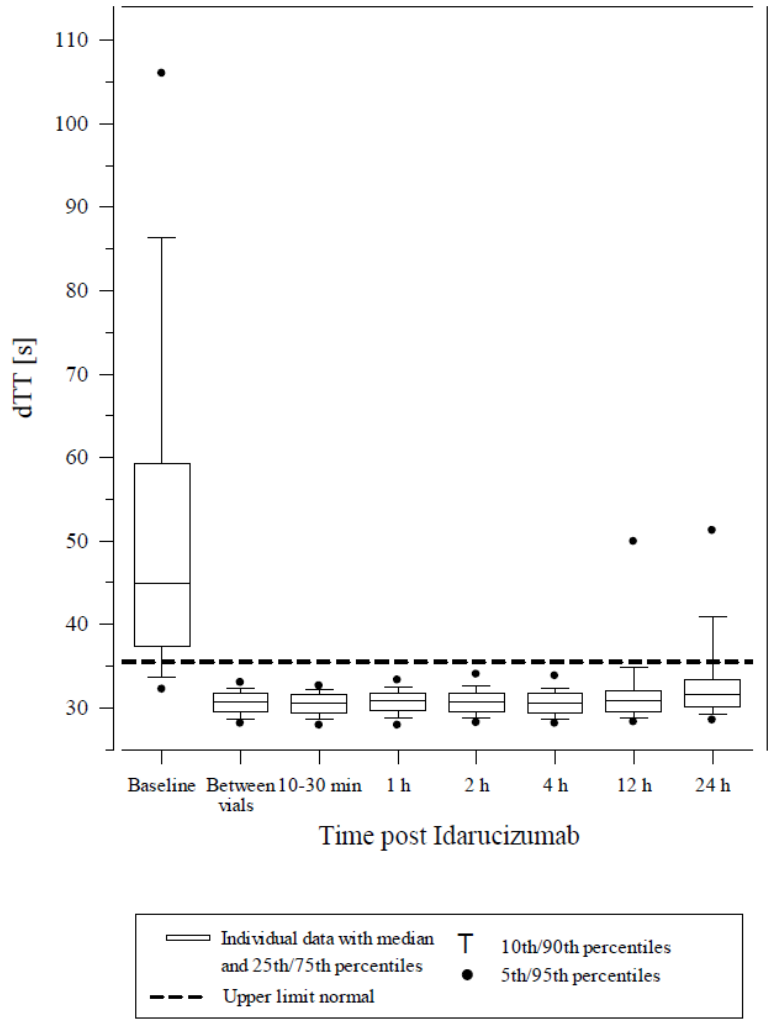

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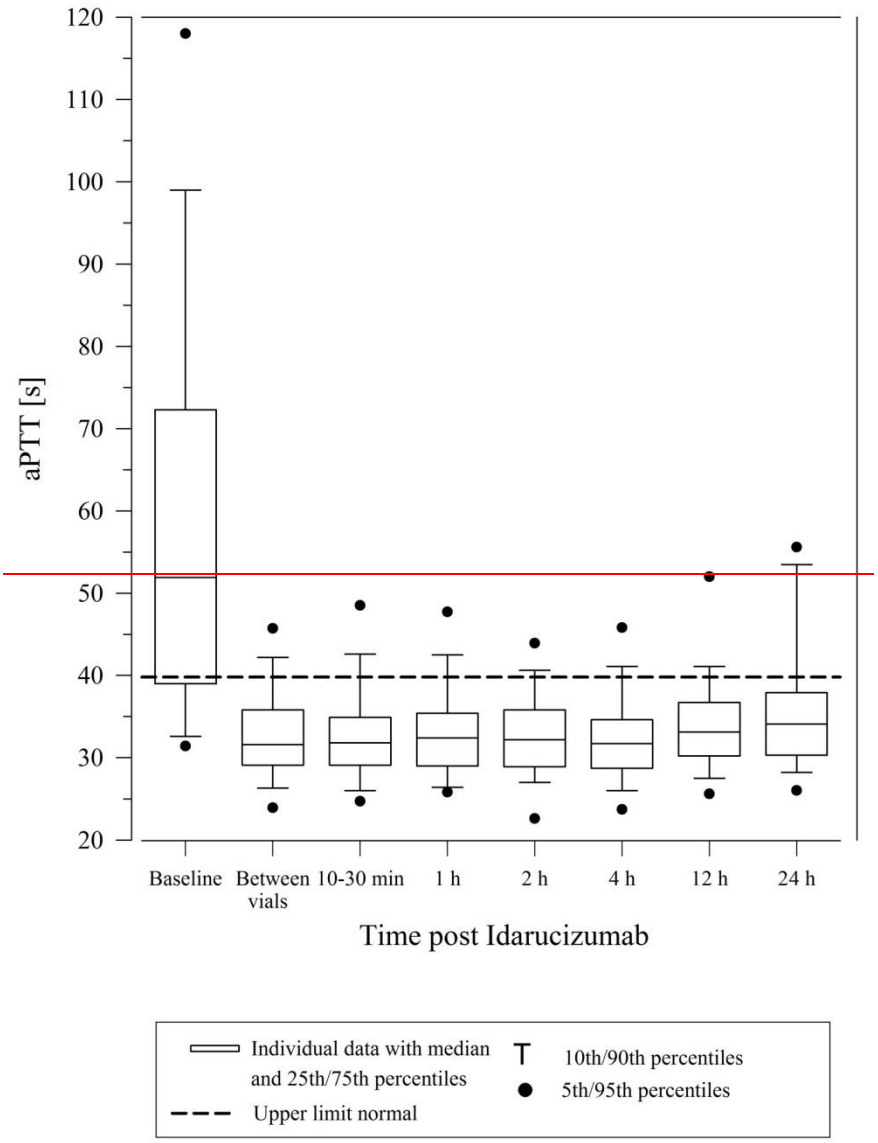
Figure 2 – Reversal of dabigatran-induced clotting time prolongation determined by ~~aPTT~~ ECT in patients from the RE-VERSE AD study (N=487) ~~in 90 patients from the RE-VERSE AD study~~



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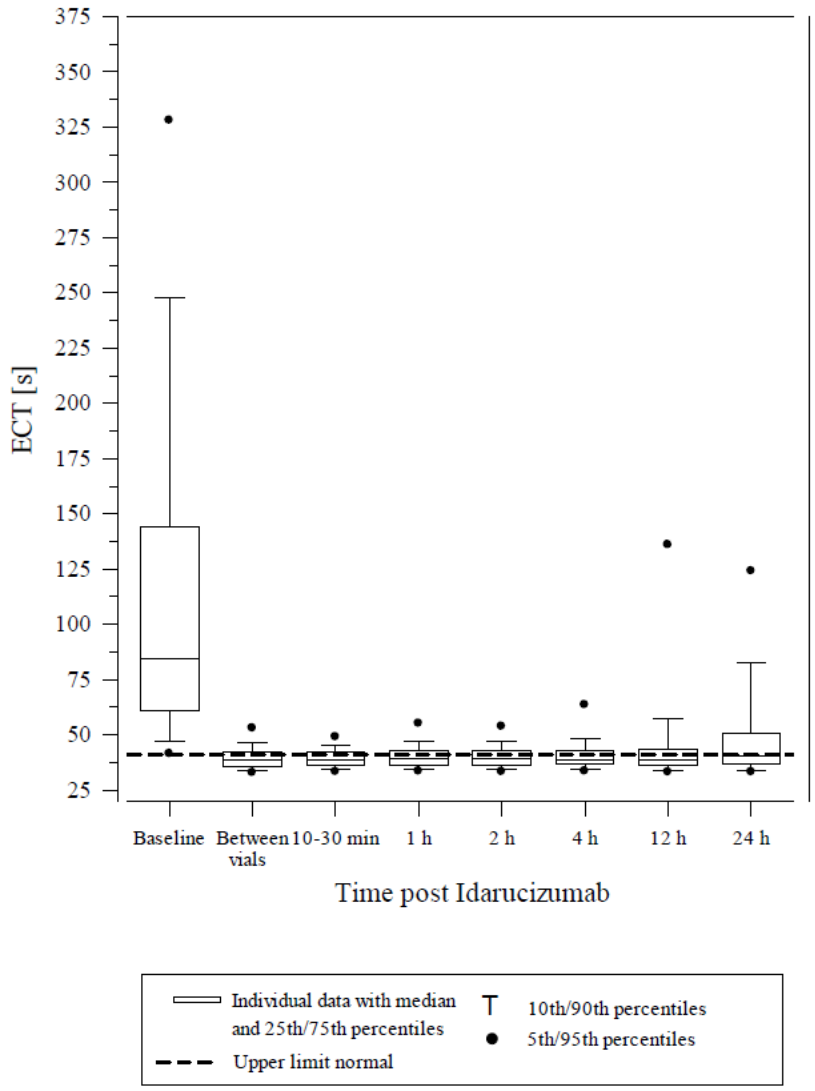

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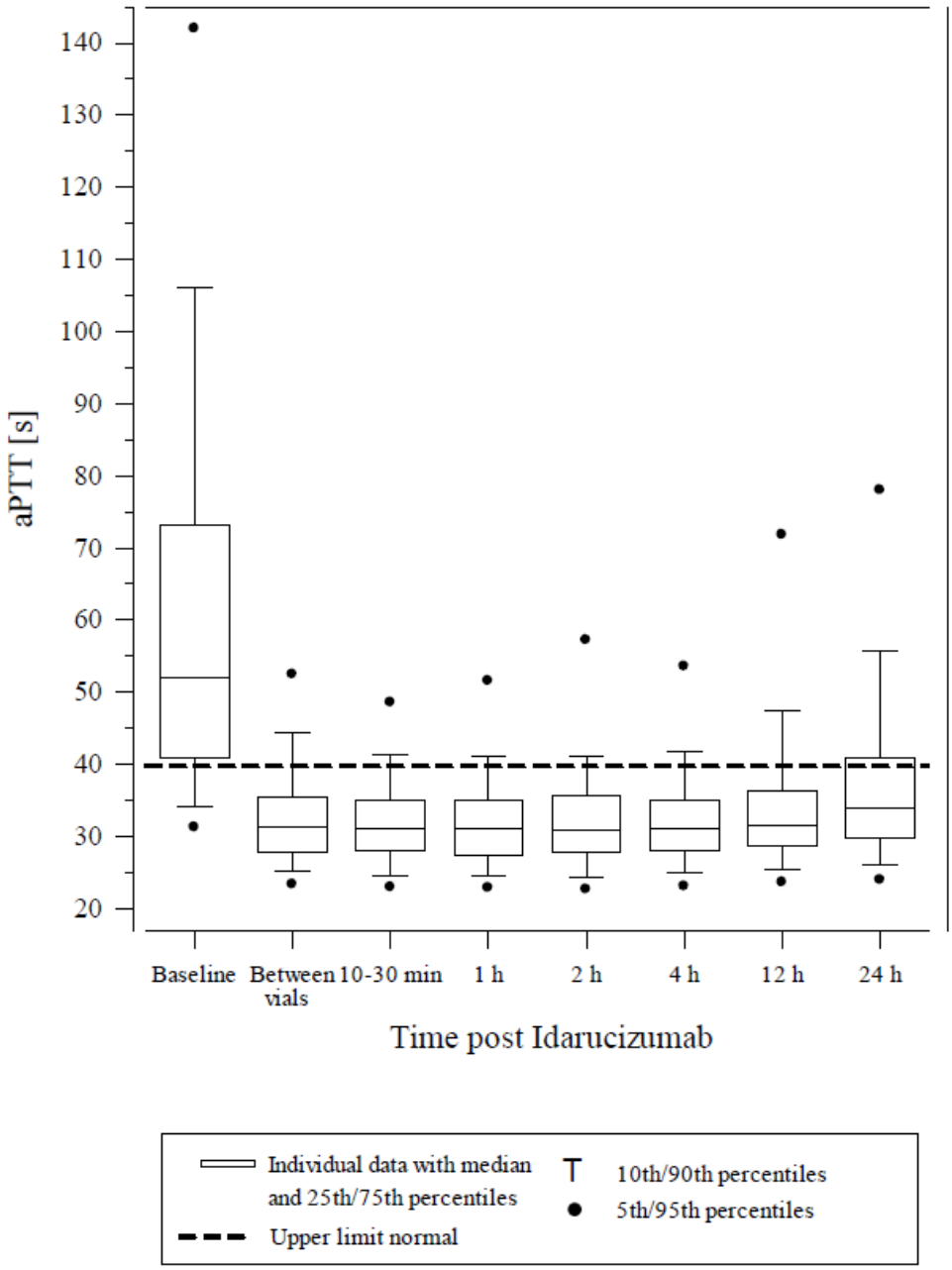
Figure 3 – Reversal of dabigatran-induced clotting time prolongation determined by aPTT in patients from the RE-VERSE AD study (N=486)



Restoration of haemostasis was achieved in ~~91~~80.3% of evaluable patients who had serious bleeding and normal haemostasis was observed in ~~92~~93.4% of patients who required an urgent procedure.

Of the total ~~123~~ 503 patients, ~~26~~ 101 patients died; each of these deaths could be attributed either as a complication of the index event or associated with co-morbidities. Thrombotic events were reported in ~~5~~ 34 patients, ~~none of which~~(23 out of the 34 patients were not on antithrombotic therapy at the time of the event)~~,~~ ~~–~~and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient. Mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported. A causal relationship to idarucizumab could not be established. ~~Further adverse~~

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~~events, reported in greater than or equal to 5% of patients, were hypokalemia (9/123; 7%), delirium (9/123; 7%), constipation (8/123; 7%), pyrexia (7/123; 6%), pneumonia (7/123; 6%).~~

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Immunogenicity

Serum samples from 283 subjects in phase I trials (224 volunteers treated with idarucizumab) and 501 patients were tested for antibodies to idarucizumab before and after treatment.

Pre-existing antibodies with cross-reactivity to idarucizumab were detected in approximately ~~13~~ 12 % (~~36~~33/283) of the phase I subjects and 3.8% (19/501) of the patients. No impact on the pharmacokinetics or the reversal effect of idarucizumab or hypersensitivity reactions were observed ~~in these subjects~~.

Treatment-emergent possibly persistent anti-idarucizumab antibodies with low titers were observed in 4 % (~~9~~10/224) of the phase 1 subjects and 1.6% (8/501) of the patients suggesting a low immunogenic potential of idarucizumab. In a subgroup of 6 phase 1 subjects, idarucizumab was administered a second time, two months after the first administration. No anti-idarucizumab antibodies were detected in these subjects prior to the second administration. In one subject, treatment-emergent anti-idarucizumab antibodies were detected after the second administration. Nine patients were re-dosed with idarucizumab. All nine patients were re-dosed within 6 days after the first idarucizumab dose. None of the patients re-dosed with idarucizumab tested positive for anti-idarucizumab antibodies.

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Patients with renal impairment

In Phase I studies Praxbind has been investigated in subjects with a creatinine clearance ranging from 44 to 213 mL/min. Subjects with a creatinine clearance below 44 mL/min have not been studied in Phase I.

Depending on the degree of renal impairment the total clearance was reduced compared to healthy subjects, leading to an increased exposure of idarucizumab.

Based on pharmacokinetic data from ~~68~~ 347 patients with different degrees of renal function (median creatinine clearance ~~19.2~~21 - ~~126~~ 99 mL/min) it is estimated that mean idarucizumab exposure (AUC_{0-24h}) increases by ~~26~~38% in patients with mild (CrCl ~~60~~50-~~90~~ <80 mL/min), by ~~78~~90% in moderate (30-~~60~~ <50 mL/min) and by ~~199~~146% in severe (0-<30 mL/min) renal impairment. Since dabigatran is also excreted primarily via the kidneys, increases in the exposure to dabigatran are also seen with worsening renal function.

Based on these data and the extent of reversal of the anticoagulant effect of dabigatran in patients, renal impairment does not ~~appear to~~ impact the reversal effect of idarucizumab~~, although the conclusion for patients with severe renal impairment is drawn from only a small subset of patients.~~.

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Patients with hepatic impairment

~~Praxbind has not been studied in patients with hepatic impairment. Antibody fragments are known to be eliminated mainly by proteolytic catabolism in the kidney.~~ An impact of hepatic impairment, assessed by hepatic injury as determined by elevated liver function tests, on the pharmacokinetics of idarucizumab has not been observed~~is not expected~~.

Idarucizumab has been studied in 58 patients with varying degrees of hepatic impairment. Compared to 272 patients without hepatic impairment, the median AUC of idarucizumab was changed by -6%, 37% and 10% in patients with AST/ALT elevations of 1 to <2x ULN (N=34), 2 to <3x ULN (N=3) and >3x ULN (N=21), respectively. Based on pharmacokinetic data from 12 patients with liver disease, the AUC of idarucizumab was increased by 10% as compared to patients without liver disease.

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