Currently available anticoagulant antidotes are protamine (for neutralization of heparin) and vitamin K for neutralization of vitamin K antagonists like warfarin. Fresh frozen plasma and recombinant factor VIIa have also been used as non-specific antidotes in patients under low molecular weight heparin treatment, suffering from major trauma or severe hemorrhage (Lauritzen, B. et al, Blood, 2005, 607A-608A.). Also reported are protamine fragments (US Patent No. 6,624,141) and small synthetic peptides (US Patent No. 6,200,955) as heparin or low molecular weight heparin antidotes; and thrombin muteins (US Patent No. 6,060,300) as antidotes for thrombin inhibitor. Prothrombin intermediates and derivatives have been reported as antidotes to hirudin and synthetic thrombin inhibitors (US Patent Nos. 5,817,309 and 6,086,871). For direct factor Xa inhibitors, inactive factor Xa analogs have been proposed as antidotes (WO2009042962). Furthermore, recombinant factor VIIa has been used to reverse the effect of indirect antithrombin III dependent factor Xa inhibitors such as fondaparinux and idraparinux (Bijsterveld, NR et al, Circulation, 2002, 106: 2550-2554; Bijsterveld, NR et al, British J. of Haematology, 2004 (124): 653-658). A review of methods of anticoagulant reversal is provided in Schulman and Bijsterveld, Transfusion Medicine Reviews 2007, 21(1): 37-48.

There is a need to provide improved antidotes for anticoagulant therapy, and in particular to provide antidotes for direct thrombin inhibitors like dabigatran for which no specific antidotes have been disclosed so far.

BRIEF SUMMARY ~~OF THE INVENTION~~

T~~In one aspect, t~~he present ~~invention~~disclosure relates to an antibody molecule capable of neutralizing the activity of an anticoagulant.

In one aspect, the present disclosure relates to an antibody molecule capable of neutralizing the activity of dabigatran, which comprises a heavy chain variable domain with a CDR1 of SEQ ID NO: 1, a CDR2 of SEQ ID NO: 7, and a CDR3 of SEQ ID NO: 10, and a light chain variable domain with a CDR1 of SEQ ID NO: 13, a CDR2 of SEQ ID NO: 14, and a CDR3 of SEQ ID NO: 15.

In ~~a further aspect~~an embodiment, the antibody molecule has binding specificity for the anticoagulant.

In ~~a further aspect~~an embodiment, the anticoagulant is a direct thrombin inhibitor, a Factor Xa inhibitor, or a vitamin K antagonist.

In a further ~~aspect~~embodiment, the anticoagulant is dabigatran, argatroban, melagatran, ximelagatran, hirudin, bivalirudin, lepirudin, desirudin, apixaban, otamixaban, edoxaban, rivaroxaban, defibrotide, ramatroban, antithrombin III, or drotrecogin alpha.

In a further embodiment, the anticoagulant is a disubstituted bicyclic heterocycle of general formula

$$R_a - A - Het - B - Ar - E \quad , (I)$$

wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido or thieno moiety of the group Het,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-4}-alkyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, phenyl-C_{1-3}-alkoxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or pyridinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a C_{1-3}-alkylsulphonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group or it denotes a 2,5-thienylene group,

Het denotes a 1-(C_{1-3}-alkyl)-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-(C_{1-3}-alkyl)-2,5-indolylene, 1-(C_{1-3}-alkyl)-

(x) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(y) 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]- aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, and

the tautomers, stereoisomers and the salts thereof.

T~~In another aspect, t~~he present ~~invention~~disclosure may relate~~s~~ to an antibody molecule against dabigatran, dabigatran exetilate, and/or an O-acylglucuronide of dabigatran.

In a further ~~aspect~~embodiment, the antibody molecule is a polyclonal antibody, a monoclonal antibody, a human antibody, a humanized antibody, a chimeric antibody, a fragment of an antibody, in particular a Fab, Fab', or $F(ab')_2$ fragment, a single chain antibody, in particular a single chain variable fragment (scFv), a domain antibody, a nanobody, a diabody, or a DARPin.

In a further aspect, the present ~~invention~~disclosure relates to an antibody molecule as described above for use in medicine.

T~~In a further aspect, t~~he present ~~invention~~disclosure may relate~~s~~ to an antibody molecule as described above for use in the therapy or prevention of side effects of anticoagulant therapy.

In a further aspect, the present disclosure relates to an antibody molecule as defined above for use in the therapy or prevention of side effects of anticoagulant therapy, and/or for reversal of an overdosing of an anticoagulant.

In a further ~~aspect~~embodiment, the side effect is a bleeding event.

T~~In a further aspect, t~~he present ~~invention~~disclosure may relate~~s~~ to a method of treatment or prevention of side effects of anticoagulant therapy, comprising administering an effective amount of an antibody molecule as described above to a patient in need thereof.

In a further aspect, the present disclosure relates to a method of manufacturing an antibody molecule as defined above, comprising

(a) providing a host cell comprising one or more nucleic acids encoding said antibody molecule in functional association with an expression control sequence,

(b) cultivating said host cell, and

(c) recovering the antibody molecule from the cell culture.

T~~In another aspect, t~~he present ~~invention~~disclosure may relate~~s~~ to a kit comprising an antibody molecule as described, together with a container and a label.

In a further aspect, the present disclosure relates to a kit comprising an antibody as defined above, or a pharmaceutical composition thereof.

In a further aspect, the present disclosure relates to a kit comprising:

(a) an antibody as defined above, or a pharmaceutical composition thereof;

(b) a container; and

(c) a label.

In a further aspect, the present disclosure relates to a kit comprising an antibody as defined above, and dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof.

In a further aspect, the present disclosure relates to a kit comprising:

(a) an antibody as defined above, or a pharmaceutical composition thereof;

(b) a pharmaceutical composition of dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof;

(c) a container; and

(d) a label.

In a further aspect, the present disclosure relates to a kit comprising:

(a) a first pharmaceutical composition comprising dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof;

(b) a second pharmaceutical composition comprising an antibody as defined above;

(c) instructions for separate admininstration of said first and second pharmaceutical compositions to a patient,

wherein said first and second pharmaceutical compositions are contained in separate containers and said second pharmaceutical composition is to be administered to a patient requiring neutralization or partial neutralization of dabigatran or 1-O-acylglucuronide of dabigatran.

In a further aspect, the present disclosure relates to an antibody as defined above, or a pharmaceutical composition thereof for use in neutralizing or partially neutralizing dabigatran or 1-O-acylglucuronide of dabigatran in a patient being treated with dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof.

In a further aspect, the present disclosure relates to a method for neutralizing or partially neutralizing dabigatran or 1-O-acylglucuronide of dabigatran comprising:

(a) confirming that a patient was being treated with dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof, and the amount that was taken by the patient;

(b) neutralizing dabigatran or 1-O-acylglucuronide in a sample taken from the patient with an antibody as defined above prior to performing a clotting or coagulation test or assay wherein dabigatran or the 1-O-acylglucuronide of dabigatran would interfere with the accurate read out of the test or assay results;

(c) performing the clotting or coagulation test or assay on a sample taken from the patient to determine the level of clot formation without dabigatran or 1-O-acylglucuronide of dabigatran present; and

(d) adjusting an amount of dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof that is to be administered to the patient in order to achieve the appropriate balance between clot formation and degradation in a patient.

25. A method for neutralizing or partially neutralizing dabigatran or 1-O-acylglucuronide of dabigatran ~~in a patient~~ comprising:

(a) confirming that a patient was being treated with dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof, and the amount that was taken by the patient;

(b) neutralizing dabigatran or 1-O-acylglucuronide in a sample taken from the patient with an antibody of any one of claims 1 to 8 prior to performing a clotting or coagulation test or assay wherein dabigatran or the 1-O-acylglucuronide of dabigatran would interfere with the accurate read out of the test or assay results;

(c) performing the clotting or coagulation test or assay on a sample taken from the patient to determine the level of clot formation without dabigatran or 1-O-acylglucuronide of dabigatran present; and

(d) adjusting an amount of dabigatran, dabigatran etexilate, a prodrug of dabigatran or a pharmaceutically acceptable salt thereof that is to be administered to the patient in order to achieve the appropriate balance between clot formation and degradation in a patient.

26. The method according to claims 24 or 25, wherein the amount of antibody to dabigatran or 1-O-acylglucuronide of dabigatran is in the molar ratio of between 0.1 and 100.

27. The method according to claim 26, wherein the amount of antibody to dabigatran or 1-O-acylglucuronide of dabigatran is in the molar ratio of between 0.1 and 10.

28. The method according to claim 25, wherein the accurate read out of the test or assay result is an accurate read out of fibrinogen levels, activated protein C resistance or related tests.