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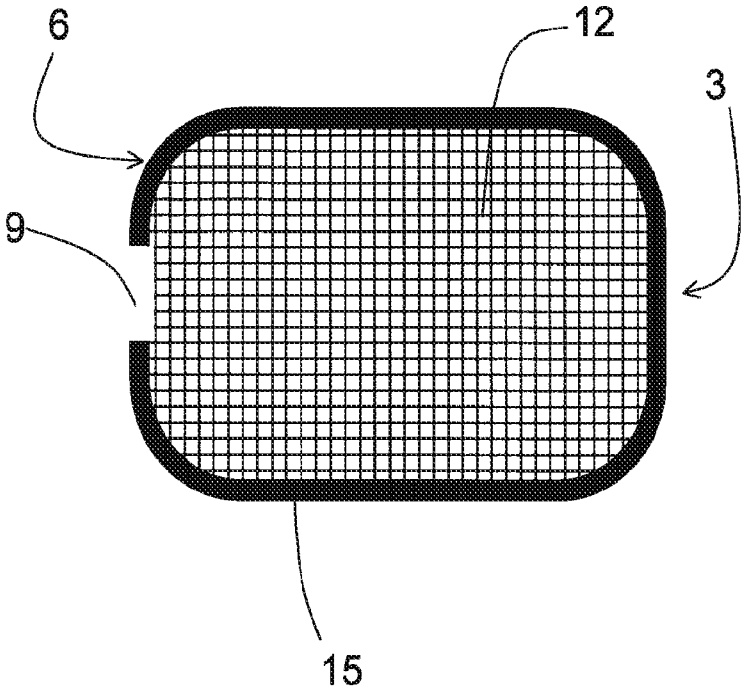
(54) Title: DOSAGE FORMS OF APIXABAN

FIG. 1



(57) Abstract: The present invention relates to a Factor Xa inhibitor dosage form comprising apixaban in a solubility-improved form wherein the dosage form provides controlled release of apixaban and methods for preventing or treating venous thromboembolisms, deep vein thrombosis and acute coronary syndrome with said dosage form.

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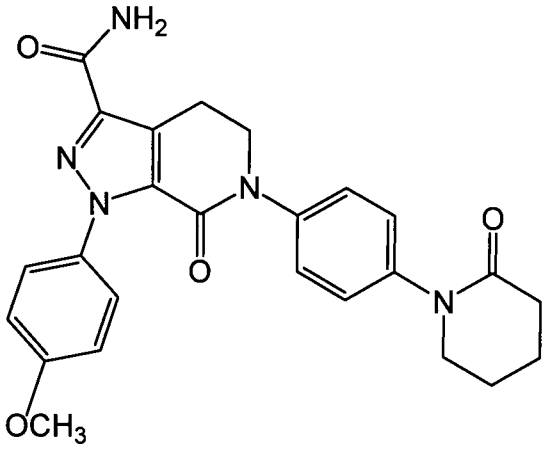
DOSAGE FORMS OF APIXABAN

BACKGROUND OF THE INVENTION

The present invention relates to a Factor Xa inhibitor dosage form comprising Apixaban in a solubility-improved form wherein the dosage form provides controlled release of Apixaban and methods for preventing or treating venous thromboembolisms, deep vein thrombosis and acute coronary syndrome with said dosage form.

Activated Factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (Factor Xa, Factor V, Ca 2+ and phospholipid). Since it is calculated that one molecule of Factor Xa can generate 138 molecules of thrombin inhibition, Factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system. Accordingly, Factor Xa inhibitors are a class of compounds that are efficacious for the treatment of thromboembolic disorders.

U.S. Patent No. 6,967,208 (hereby incorporated by reference) discloses a series of Factor Xa inhibitors including 1H-Pyrazolo[3,4-c]pyridine-3-carboxamide,4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-; alternatively named as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3.4-c]pyridine-3-carboxamide (hereinafter referred to as apixaban). The structure of apixaban is



U.S. Pat. No. 6,967,208 discloses that the compounds of the invention may be administered in the form of a pharmaceutical composition comprising at least one of the compounds, together with a pharmaceutically acceptable vehicle, diluent, or carrier. For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders and the like. Apixaban has been provided as a twice daily administration. WO 2007/022165 discloses an injectable Factor Xa (e.g., apixaban) formulation. WO 2006079474 and WO2008066102 disclose sustained release Factor Xa inhibitor formulations. WO2008031782 discloses modified release Formulations of Factor Xa inhibitors. Further pharmaceutical dosage forms are described in EP 1653926.

There is a continuing need to find safe, effective methods of delivering Factor Xa inhibitors including abixaban.

SUMMARY OF INVENTION

The present invention is directed to a solubility-improved form of apixaban wherein the dosage form provides controlled release of apixaban, designated the A dosage form.

A preferred aspect of the A dosage form is a controlled release dosage form that releases *in vivo* or *in vitro* 70 wt% of apixaban over 2 hours or more after administration of the dosage form to an aqueous environment of use.

Another preferred aspect of the A dosage form, designated the B dosage form, is an osmotic controlled release dosage form.

A preferred aspect of the B dosage form, designated the C dosage form, is a bilayer osmotic controlled release dosage form.

Another preferred aspect of the A dosage form is a dosage form wherein following administration to an in vivo use environment, the dosage form provides a plasma concentration of apixaban of about 70 ng/mL or more for a period of about 12 hours or more.

Yet another preferred aspect of the A dosage form is a dosage form wherein the solubility-improved form is selected from the group consisting of a solid amorphous dispersion, lipid vehicle comprising apixaban, a solid adsorbate comprising apixaban adsorbed onto a substrate, nanoparticles, adsorbates of apixaban in a crosslinked polymer, a nanosuspension, a supercooled form, an apixaban/cyclodextrin drug form, a softgel form, a self-emulsifying form, a three-phase apixaban form, a crystalline highly

soluble form, a high-energy crystalline form, a hydrate or solvate crystalline form, an amorphous form, a mixture of apixaban and a solubilizing agent, and a solution of apixaban dissolved in a liquid.

Yet another preferred aspect of the A dosage form, designated the D dosage form is a dosage form wherein said solubility-improved form is a solid amorphous dispersion comprising apixaban and a polymer.

A preferred aspect of the D dosage form is a dosage form wherein the solid amorphous dispersion is a spray-dried dispersion.

A preferred aspect form of the C dosage form, designated the E dosage form, is a dosage form wherein the osmotic controlled release dosage form comprises a solid amorphous dispersion comprising apixaban and a polymer.

A preferred aspect of the E dosage form, designated the F dosage form, is a dosage form wherein the solid amorphous dispersion comprising apixaban and a polymer is a spray-dried dispersion.

A preferred aspect of the F dosage form, designated the G dosage form, is a dosage form wherein the osmotic controlled release dosage form comprises a bilayer tablet comprising an orifice.

A preferred aspect of the G dosage form is a dosage form wherein following administration to an in vivo use environment, the dosage form provides a plasma concentration of apixaban of about 70 ng/mL or more for a period of about 12 hours or more.

Yet another preferred aspect of the A dosage form, designated the H dosage form, is a dosage form wherein the controlled release dosage form is a matrix controlled release dosage form.

A preferred aspect of the H dosage form is a dosage form wherein the matrix controlled release dosage form comprises a solid amorphous dispersion comprising apixaban and a polymer and the solid amorphous dispersion is a spray-dried dispersion.

A preferred aspect of the A dosage form is a dosage form having an in-vitro dissolution rate, wherein the in-vitro dissolution rate is wherein less than about 10 wt% apixaban is released by one hour, about 20 wt% apixaban to about 40 wt% apixaban is released by four hours, about 60 wt% apixaban to about 80 wt% apixaban is released at about eight hours, and more than about 70 wt% apixaban is released at ten hours.

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