Title: CLOPIDOGREL FOR USE IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

Abstract: The present invention relates to the novel use of clopidogrel and pharmaceutically acceptable salts thereof. More precisely, the invention relates to the use of clopidogrel and pharmaceutically acceptable salts thereof against benign prostatic hyperplasia. Specifically, the invention relates to clopidogrel and its pharmaceutically acceptable salts for use in the treatment of benign prostatic hyperplasia (BPH), and to the use of clopidogrel and its pharmaceutically acceptable salts for the preparation of a pharmaceutical composition useful for the treatment of benign prostatic hyperplasia. Further, the invention also relates to a pharmaceutical composition for the use in the treatment of BPH, comprising clopidogrel or its pharmaceutically acceptable salts as active ingredient.
CLOPIDOGREL FOR USE IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

FIELD OF THE INVENTION

The present invention relates to the novel use of clopidogrel and pharmaceutically acceptable salts thereof. More precisely, the invention relates to the use of clopidogrel and pharmaceutically acceptable salts thereof against benign prostatic hyperplasia. Specifically, the invention relates to clopidogrel and its pharmaceutically acceptable salts for use in the treatment of benign prostatic hyperplasia (BPH), and to the use of clopidogrel and its pharmaceutically acceptable salts for the preparation of a pharmaceutical composition useful for the treatment of benign prostatic hyperplasia. Further, the invention also relates to a pharmaceutical composition for the use in the treatment of BPH, comprising clopidogrel or its pharmaceutically acceptable salts as active ingredient.

BACKGROUND OF THE INVENTION

Prostatic diseases form the major group of men’s diseases. Prostate is a small round gland located before the rectum, under the bladder. Its primary function is to secrete an excretion into the urethra upon ejaculation. During ejaculation semen from the testicles pass through the spermatic duct. The spermatic duct passes the bladder from behind and runs into the prostate. Upon passing through the genitalia, semen admixes with the spermatic excretion, the other component of the ejaculate, originating from three sources: the seminal vesicles, the prostate and the Cowper glands. With this, the ejaculate passes through the urethra and leaves the body through the penis.

Prostate undergoes several changes during a man’s life. At birth, it has approximately a size of a pea. It grows slowly during childhood, shows a rapid growth at puberty and reaches the size and form typical for a normal adult man at an age around 20. Its size remains usually unchanged till an age of 40-50, followed by a further growth at most men. This change, the benign prostatic growth, also called as benign prostatic hyperplasia (BPH) is the most common benign tumorous disease of men, which becomes more frequent with the age and significantly
influences their health and quality of life. Most men suffer from prostatic hyperplasia but only their small proportion receives proper treatment. 20% of men at an age 40 to 64, and 40% of men over the age of 65 faces this problem. The occurrence of BHP among men over 60 is 50, increasing to 88 among men over the age of 80.

BHP may cause several urination problems. BHP develops, when the number of the cells within the prostate starts to increase causing thereby the growth of the gland itself. This growth occurs slowly and gradually. Most men do not even recognize the symptoms of the enlargement of the prostate only at the point when their uresis changes. The sensible change of the uresis is the common symptom of the enlargement of the prostate which is caused by the compression of the urethra and the impairment of the of the bladder function. One cause of the compression of the urethra is that upon enlargement of the prostate it exerts a certain pressure on the wall of the urethra, which narrows, slowing thereby the uresis. Further, the prostate also contains smooth muscles, which can contract unwillingly and exert thereby also a pressure on the urethra, which may influence the normal uresis as well. Development of BHP may also cause changes in the musculature of the bladder wall.

The disease can be concluded from various symptoms said symptoms being practically typical: frequent, urging urination stimulus, inconvenient urination inducible by pressing, weak and erratic urinary flow, bladder pain, incontinence problems, post urination ooze and in more severe cases the stagnation of the urination in the bladder may be an indicator for the illness which often leads to pain and restraint of the sexual activity. Untreated prostatic hyperplasia may lead to the infection of the urethra, damage of the bladder and the kidney, formation of bladder stone formation and incontinence.

Examination of the diseases concerning prostate are carried out in more stages. The first stage is usually a normal prostate examination. From the tactile find the attending physician is able to make a conclusion regarding the eventual disease concerning the prostate. This may be followed by an ultrasound examination or even by a blood test. In the latter case, the sample is analyzed for a special protein
called PSA (prostate-specific antigen), the serum level of which may indicate the status of the prostate. If the measured level is higher than the normal level it may indicate a disease of the prostate. The blood test is an important part of the examination procedure, since the symptoms of BPH may be very similar to those of the prostatic cancer, which can be definitely identified via blood test. In other words, such an examination may help in distinguishing the benign and malignant diseases of the prostate. Based on the examination results, the physician suggests a proper treatment method usually considering the quality and the severity of the symptoms.

From publication, belonging to the state of art several methods for the treatment of BPH are known.

EP 1480634 describes a method for treating BPH. More precisely, the invention provides a method of treating, preventing, suppressing, inhibiting or reducing the incidence of benign prostate hyperplasia in a male subject, by administering to the subject a selective androgen receptor modulator (SARM) and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, hydrate, N-oxide, or any combination thereof as described herein. This invention also provides a method of treating a subject suffering from hair loss, comprising the step of administering to the subject a therapeutically effective amount of a 5-a reductase enzyme type 1 and/or type 2 inhibitor, wherein said inhibitor is a selective androgen receptor modulator (SARM) and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, hydrate, N-oxide, or any combination thereof.

International Publication No. WO 99/42488 discloses substituted heterocyclic piperazines with formula (I) below
methods of treatment, pharmaceutical compositions containing them, and intermediates used in their manufacture. The compounds of the invention are useful in the treatment of BPH. The compounds of the invention selectively inhibit binding to the alpha-1a adrenergic receptor, a receptor which has been implicated in benign prostatic hyperplasia.

International Publication No. WO 99/42445 describes phthalimidoarylpiperazine with alpha-1a receptor antagonist activity having the following general formula

![Chemical Structure](image)

as well as pharmaceutical compositions containing the same or intermediers thereof.

The compounds of the invention are also useful for the treatment of BPH. The compounds selectively inhibit the binding on alpha-1a adrenerg receptor, said receptor associated with benign prostatic hyperplasia. In general formula (I) the substituents are as follows:

- $R_1$ is hydrogen or halogen, C$_1$-C$_6$ alkoxyl, hydroxyl or C$_1$-C$_6$ alkyl,
- $R_2$ is optionally substituted C$_1$-C$_6$ alkyl, phenyl or phenyl-C$_1$-C$_6$ alkyl,
- $R_3$ is hydrogen, hydroxyl or C$_1$-C$_6$ alkoxyl,
- $R_4$ is hydrogen, C$_1$-C$_6$ alkyl, phenyl or phenyl-C$_1$-C$_6$ alkyl;
- $R_5$, $R_6$ and $R_7$ are hydrogen or halogen, hydroxyl or optionally substituted C$_1$-C$_6$ alkyl or C$_1$-C$_6$ alkoxyl, amino, alkylcarbonyl or alkoxycarbonyl,
- A, B, E are N or C, with the proviso that only one of them can be nitrogen.
International Publication No. WO97/00069 describes the use of melatonin agonists for the preparation of pharmaceutical compositions useful for the treatment of BPH. Said pharmaceutical compositions comprise a compound with melatonin agonist activity as active ingredient together with carriers, diluents and excipients. Said melatonin agonist active ingredient may be for example an N-[2-(substituted 3-indoly)-ethyl]-amide, substituted N-[2-(heteroaryl)-ethyl]-amide, N-[2-(substituted 1-naphthyl)-ethyl]-amide, N-[substituted 1,2,3,4-tetrahydro-2-naphthyl]-amide or N-[substituted 1,2,3,4-tetrahydro-9H-carbazol-4-yl]-methyl]-amide and especially an N-[2-(substituted 3-indoly)-ethyl]-amide of the general formula (I)

\[
\text{wherein}
\]
\[
R^1 \text{ is H, C}_1\text{-C}_4 \text{ alkyl or C}_1\text{-C}_4 \text{ alkoxy;}
\]
\[
R^2 \text{ is H or C}_1\text{-C}_4 \text{ alkyl;}
\]
\[
R^3 \text{ is H, C}_1\text{-C}_4 \text{ alkyl, phenyl or substituted phenyl;}
\]
\[
R^4 \text{ is H, haloacetyl, C}_1\text{-C}_3 \text{ alkanoyl, benzoyl or a benzoyl substituted by halo or methyl;}
\]
\[
R^5 \text{ and } R^6 \text{ are each H or halo;}
\]
\[
R^7 \text{ is H or C}_1\text{-C}_4 \text{ alkyl.}
\]

International Publication No. WO 2014014177 describes a method wherein as an agent for preventing and treating benign prostatic hyperplasia Dendropanax moribifera extract or a compound which is isolated from the extract and then purified is used. According to the invention, the extract and the compound have been demonstrated to be capable of preventing benign prostatic hyperplasia through a mechanism for inhibiting the androgen receptor signaling that induces benign prostatic hyperplasia.
International Publication No. WO 2012145714 describes monospecific and multispecific polypeptide therapeutic agents capable of specifically targeting cells expressing prostate-specific membrane antigen (PSMA) said agents being therefore suitable among others also for the treatment of BPH. According to one embodiment of the invention the multispecific polypeptide therapeutic agents are capable of binding both PSMA expressing cells and T-cell receptor complexes on the T-cells, to induce target-dependent T-cell cytotoxicity, activation and proliferation.

International Publication No. WO 2011004260 describes a pharmaceutical composition comprising 9 to 40 mg of degarelix or the pharmaceutically acceptable salts thereof together with a solvent where the concentration of degarelix or its salt is 35 to 45 mg/ml. The invention also relates to a method for the preparation of said composition as well as a kit comprising said composition.

International Publication No. WO 2009070818 relates to the use of at least one protease for the preparation of a medicament suitable for the treatment and/or prevention of BPH, wherein the medicament is adapted for enteral administration, the at least one protease is selected from the group consisting of plant, non-mammalian animal and microbial proteases and the at least one protease is administered in an amount of 1 to 100 mg/kg body weight.

In addition to the above, as far as the actual treatment of BPH is concerned, the various medical interventions can be carried out depending on the stage of the disease. In case of rather mild symptoms, medication of the patient is not justified. Of most importance are the regular half-year examinations, during which the urinary flow and the residual urine are controlled. At this stage certain changes in the manners, reduced consumption of liquids in the evening, reduced consumption of coffee or tea may ameliorate the symptoms. A possible way of the treatment is the use of plant extracts. Although their way of action is only partially known they usually ameliorate the mild symptoms due to their anticongestive, antioedemic and anti-inflammatory effects. Their side-effects are neglectable. They are very popular in Europe, especially in Germany, but also in France and Italy, and are widely used. As mentioned above for the treatment S-alpha reductase inhibitors are also used, one
outstanding member of said compound group being finasteride. Several studies proved that a 5 mg daily dose of finasteride reduces the volume of the prostate by 20-30 % after a treatment of few months, usually after a 6-months treatment, thereby reducing the residual urine, ameliorating the symptoms of the patient and improving his quality of life. As also mentioned before, alpha blockers are used for the treatment as well. By blocking the corresponding alpha receptors, the smooth muscle tonicity can be reduced, which results in better passage of the bladder and better urinary flow. Alpha blockers exert their action quickly, within a few days. The most common treatment method is, however, the operation. Although it is the most common urological operation, technically it is not simple, which is proven by its morbidity, and the non-decreasing rate of its short-term and long-term complications.

Since - according to the above - BPH affects a significant part of the male population, and the most common treatment method - the operation - involves high risks, further, since it is generally known that individual patients react differently to the administered active substances, it is desirable to broaden the treatment possibilities of the disease, and therefore, it is obvious that developing more methods for the treatment, prevention, inhibition or reducing BPH is needed.

The inventors surprisingly found that clopidogrel, a well-known active substance successfully used in other indication can be effective for the treatment of BPH.

Clopidogrel is a well-known thrombocyte aggregation inhibitor and antithrombotic drug. It is useful in the treatment and prevention of various thrombocyte-associated vascular diseases.

Clopidogrel, by its chemical name methyl-(S)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5-(4H)-acetate (CAS No. 113665-84-2) has the following structure:
Clopidogrel, just like most pharmaceutically active ingredients - is used in the form of its pharmaceutically acceptable salts, for example as clopidogrel hydrochloride (CAS No. 120202-65-5), clopidogrel hydrobromide (CAS No. 120202-67-7), clopido-grel hydrogensulfate also known as clopidogrel bisulfate (CAS No. 120202-66-6), clo-pidogrel mesylate (CAS No. 744256-72-2) and clopidogrel bezilate (CAS No. 7744256-69-7).

The preparation of clopidogrel is described for example in European Patent No. 0 099 802 B1. Preparation of the pharmaceutically acceptable salts may be carried out for example according to the methods disclosed in European Patent Application No. EP 0 281 459 A. European Patent No. EP 1 756 116 describes various polymorphs of clopidogrel hydrobromide (forms A to D), while European Patent No. 1 087 976 discloses two polymorphs of clopidogrel hydrogensulfate (forms I. and II.).

According to the above clopidogrel is a well-known compound which is used for example as active ingredient of pharmaceutical compositions distributed under the names Plavix® and Iscover®. Said compositions comprise one of the pharmaceutically acceptable salts of clopidogrel, the hydrogensulfate salt in an amount corresponding to 75 mg free base, and are formulated as tablets. The marketed compositions in tablet form comprise hydrogenated castor oil, low-substituted hydroxypropylcellulose, mannit, microcrystalline cellulose and polyethylene glycol 6000 as auxiliaries. The tablets are usually provided with a coating for the proper release of the active substance. One preferable release profile known from the state of art is at least 80% in 1000 ml solution having a pH value of 2.0, stirred at 50 1/min with a propeller mixer.

European Patent No. 2095815 B1 relates to novel stable pharmaceutical compositions for oral administration of clopidogrel and its pharmaceutically
acceptable salts. More precisely, the invention relates to pharmaceutical compositions for oral use in tablet form comprising a pharmaceutically acceptable salt of clopidogrel and isomalt. The document describes that clopidogrel is effective for the treatment and prevention of various vascular diseases, for example stroke, arteriosclerosis, myocardial infarction, angina pectoris, arrhythmia, peripheral arterial diseases and Burger disease. According to the invention clopidogrel decreases the chance of arterial closure through inhibition of thrombocyte aggregation.

European Patent No. EP1480985 B1 describes a benzosulfonic acid salt comprising clopidogrel, a process for the preparation of the same as well as the use of the compound for the preparation of pharmaceutical compositions. The invention also relates to active ingredient particles comprising clopidogrel besylate. According to the invention clopidogrel inhibits the platelet aggregation and is therefore useful for the prevention of thromboembolic events, for example stroke of myocardial infarction.

Hungarian Patent Application No. P 0200438 discloses Form I and Form II clopidogrel methyl- and ester hydrochlorides and hydrates, pharmaceutical compositions comprising the compounds as well as the preparation of the same. According to the invention and the specification the new polymorphs possess anti-platelet aggregation and antithrombotic effect.

International Publication No. WO99/65915 relates to a novel orthorhombic form of clopidogrel hydrogen sulfate, to pharmaceutical compositions comprising the same as well as to a preparation method thereof. According to the specification the compounds possess outstanding anti-platelet aggregation and antithrombotic effect.

International Publication No. WO97/29753 describes synergic pharmaceutical compositions comprising a combination of clopidogrel and an antithrombotic agent as active ingredient. The pharmaceutical compositions according to the invention are suitable for the treatment of diseases associated with platelet aggregation. More precisely, the invention relates to pharmaceutical compositions comprising a novel combination anti-platelet aggregation combination, said combination comprising clopidogrel and aspirin.
US Patent Application No. US 2004180812 discloses methods of treating proliferative disease said treatment comprising administering, concurrently or sequentially, an effective amount of an anti-platelet or anti-clotting agent and an anti-neoplastic agent and/or radiation therapy. A second method of treatment comprises administering Plavix, also known as clopidogrel, to a patient in need of such treatment. An additional method comprises administering an anti-platelet or anti-clotting agent to an individual at risk for developing proliferative disease. The methods of the present invention are particularly useful for the treatment or prevention of various cancers, especially epithelial cancers, e.g., prostate cancer, lung cancer, breast cancer, colorectal cancer, and pancreatic cancer. In preferred embodiments, the anti-platelet agent is combined with one of the following antineoplastic agents: taxotere, gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytoxin®), temozolomide, or Vincristine.


International Publication No. WO2005/070464 discloses a tablet formulation comprising clopidogrel bisulfate said formulation comprising hydrogenated vegetable oil as diluent and microcrystalline cellulose and lactose monohydrate as excipients.

European patent No. 1310245 describes pharmaceutical tablets comprising clopidogrel bisulfate and a lubricant selected from zinc stearate, stearic acid, and sodium stearyl fumarate. Said tablets contain methylcellulose as excipient. On basis of the teaching of the specification the tablets are preferably free from microcrystalline cellulose inhibiting the release of the active substance.

International Publication No. WO2007/008045 discloses clopidogrel bisulfate compositions comprising hydrogenated castor oil and sodium stearyl fumarate as lubricant and microcrystalline cellulose, starch and mannitol as diluents.

International Publication No. WO2007/049868 describes pharmaceutical
compositions containing clopidogrel hydrogensulfate, where in the compositions starch and cellulose are used in a determined ratio.

International Publication No WO2007/091279 discloses compositions comprising clopidogrel hydrogensulfate as active ingredient, said compositions containing glycerin dibehenate as lubricant and anhydrous lactose and microcrystalline cellulose as diluent.

European Patent No. 1 847 258 discloses compositions comprising clopidogrel and partially protected glycerine.

As it is mirrored by the state of art, it is well known that clopidogrel can be used successfully for preventing and treating various vascular diseases associated with thrombocytes. As such diseases the state of art mentions arteriosclerosis, angina pectoris, arrhythmia, and peripheral arterial diseases. However, there is no suggestion in the state of art regarding the successful use of clopidogrel for the treatment of benign prostatic hyperplasia (BPH)

DETAILED DESCRIPTION OF THE INVENTION

As mentioned before, the inventors of the present invention surprisingly found that clopidogrel, a well-known active ingredient used successfully in other indications may be useful for the treatment of BPH

More precisely, the present invention bases in the recognition that administering clopidogrel or its pharmaceutically acceptable salt to a patient in the need thereof the symptoms of the benign prostatic hyperplasia can be improved, ameliorated or ceased.

According to the above, the present invention relates to the novel use of clopidogrel and its pharmaceutically acceptable salts. More precisely, the invention relates to clopidogrel and its pharmaceutically acceptable salts for use in the treatment of benign prostatic hyperplasia (BPH).

The invention also relates to the use of clopidogrel and its pharmaceutically acceptable salts for the preparation of a pharmaceutical composition useful for the
treatment of benign prostatic hyperplasia.

Further, the invention also relates to a pharmaceutical composition for the use in the treatment of BPH, comprising clopidogrel or its pharmaceutically acceptable salts as active ingredient. Said pharmaceutical composition comprises preferably the hydrochloride salt or the bisulfate salt as pharmaceutically acceptable salt. In the pharmaceutical compositions clopidogrel or its pharmaceutically active salts are use in an amount of 75 mg calculated for the free base.

A very important feature of the present invention is that the inventors discovered not only a novel use of clopidogrel but overcame also a general professional prejudice by using clopidogrel against BPH. Namely, several studies suggest that clopidogrel does not reduce the symptoms of BPH; to the contrary, it may even cause BPH. This fact is suggested for example by documents published under the following links:


http://medsfacts.com/study-CLOPIDOGERL%20BISULFATE-causing-
BENIGN%20PROSTATIC%20HYPERPLASIA.php, http://www.e-heal-th-
me.com/ds/clopidogrel+bisulfate/bph.

In order to prove their theory the inventors conducted biological test on volunteers. During the tests the PSA levels of the samples were determined. As mentioned above PSA or the prostate-specific antigen is indicative to various - both benign and malignant - changes in the status of the prostate.

PSA is expressed primarily in the gland epithelium of the prostate, and due to its ooze from the gland it is also detectable in the blood at a certain level. The increase of the serum PSA level is due to the diseases of the prostate, among others also due to the benign prostatic hyperplasia. PSA level provides information on several characteristic of the prostate, of its size and status. In accordance with the above, the PSA level will be determined from blood samples. The PSA level may increase with the age, in case of prostatitis, benign prostatic hyperplasia (BPH) or malignant
states of the prostate (prostatic cancer), however, it has to be noted that cycling, horse riding, ejaculation or medical examination before blood test may contribute to elevated serum PSA levels. However, obviously, the elevated PSA level generally suggests an increase in the volume of the prostate.

5 EFFECT OF CLOPIDOGREL ON PROSTATE SPECIFIC ANTIGENE (PSA)

The aim of the present study was to retrospectively evaluate the effect of 75 mg once daily clopidogrel on the total Prostate Specific Antigen (tPSA) in male patients between age of 45 and 60.

Study design: The study was an open design in an outpatient setting, where male patients between the age of 45 and 60 were examined due to cardiological conditions without any prostate or lower urinary tract complaints. After collecting anamnestic data and physical examination all of them were prescribed once daily 75 mg clopidogrel. No other medication was taken by or prescribed to the patients. During the medical check up a routine tPSA determination was carried out, which was repeated at a follow-up examination two month later (range 54-63 days). The tPSA was determined by ELISA test during normal blood test for other parameters. The tPSA values of the original and the follow-up tests were compared.

Results:

<table>
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<tr>
<th>Subject</th>
<th>Baseline tPSA ng/ml</th>
<th>Follow-up tPSA ng/ml</th>
</tr>
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<tr>
<td>1</td>
<td>4,4</td>
<td>3,7</td>
</tr>
<tr>
<td>2</td>
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<td>8</td>
<td>3,4</td>
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</table>

The results obtained clearly show that there was a statistical difference between the tPSA levels between baseline and follow-up. This proves that administering a daily dose of already 75 mg - as indicated by the decrease of the tPSA value, an
improvement in the symptoms characteristic to BPH occurred, which clearly indicates that the active ingredient of the tests can be used successfully for the treatment of BPH.

According to the above, for the use of the present invention clopidogrel or its pharmaceutically acceptable salts can be formulated into the corresponding pharmaceutical compositions. The compositions can be prepared via methods generally known for a person skilled in the art.

For the preparation of the pharmaceutical compositions for the purposes of the present invention clopidogrel and its pharmaceutically acceptable salts are typically formulated into compositions for oral use, preferably into tablets. Although the tablet form is preferred due to the good bioavailability of clopidogrel and its pharmaceutically acceptable salts, it is obvious for a person skilled in the art that if, desired, said active ingredients can be formulated arbitrarily into any known further administration forms suitable for the indication of the present invention commonly used for clopidogrel and its pharmaceutically acceptable salts.

For oral administration clopidogrel or its pharmaceutically acceptable salts can be readily formulated by combining said active ingredients and pharmaceutically acceptable excipients well-known in the art. Said excipients enable the formulation of clopidogrel and its pharmaceutically acceptable salts into tablets, pills, coated tablets, capsules, liquids, syrups, suspensions etc. for oral use for the patient in need thereof. For oral forms like powders, capsules and tablets the suitable excipients include fillers, for example sugars, i.e. lactose, sucrose, mannitol and sorbitol; cellulose products, like corn starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; granulating agents and binders. If desired, disintegrants can be also added, such compounds are crosslinked polyvinylpirrolidones, agar or alginic acid, or the salts thereof, for example sodium alginate. If desired, the solid unit dosage forms can be provided with a sugar coating or an enteral coating, by using standard techniques. For the indication of the present invention clopidogrel or its pharmaceutically acceptable salts are administered typically in the form of tablets.
The invention provides a further possibility to treat BPH affecting the majority of the male population. The use of the invention has the advantage that the most common treatment method, the quite riskful surgery can be omitted, and due to the good bioavailability of the active ingredient already low doses are sufficient for the successful treatment, i.e. the drug load of the patient's system can be maintained at sufficiently low level. A further important feature of the present invention is that the inventors overcame also a general professional prejudice: they not only discovered a novel use of clopidogrel but opposed a general assumption suggested by the state of art according to which clopidogrel may even be a cause for BPH.
CLAIMS


2. Clopidogrel or its pharmaceutically acceptable salts for the use according to claim 1, wherein clopidogrel or its pharmaceutically acceptable salt is used in an amount of 75 mg/day calculated for the free base.

3. Clopidogrel or its pharmaceutically acceptable salts for the use according to claim 2 wherein the 75 mg/day dose of the active ingredient is administered in a single dose.

4. Clopidogrel or its pharmaceutically acceptable salts for the use according to any of claims 1 to 3 wherein the pharmaceutically acceptable salt is the hydrochloride salt or the bisulfate salt.

5. Use of clopidogrel or its pharmaceutically acceptable salts for the preparation of a pharmaceutical composition useful for the treatment of benign prostatic hyperplasia (BPH).

6. Use according to claim 5 wherein clopidogrel or its pharmaceutically acceptable salt is used in an amount of 75 mg/day calculated for the free base.

7. Use according to claim 6 wherein the 75 mg/day dose of the active ingredient is administered in a single dose.

8. Pharmaceutical composition comprising clopidogrel or its pharmaceutically acceptable salts thereof for use in the treatment of BPH.
9. Pharmaceutical composition according to claim 8 comprising clopidogrel or its pharmaceutically acceptable salt in an amount of 75 mg/day calculated for the free base, as active ingredient.

10. Pharmaceutical composition according to claim 8 or 9 in tablet form.

11. Use according to any of claims 5 to 7 or the pharmaceutical composition according to any of claims 8 to 10 wherein the pharmaceutically acceptable salt of clopidogrel is the hydrochloride salt or the bisulfate salt.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4365 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>KEVIN S. CHOE ET AL: &quot;The use of anticoagulants improves biochemical control of localized prostate cancer treated with radiotherapy&quot;, CANCER, vol. 116, no. 7, 1 April 2010 (2010-04-01), pages 1820-1826, XP55209223, ISSN: 0008-543X, DOI: 10.1002/cncr.24890 See also Abstract; page 1821, column 1, lines 13-17, paragraph 3 page 1822, column 1, paragraphs 2,3 page 1823, paragraph 3 page 1824, column 2, paragraph 2 ------ ----</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

* Further documents are listed in the continuation of Box C.

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
31 August 2015

Date of mailing of the international search report
08/09/2015

Name and mailing address of the ISA/
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Fax (+31-70) 340-3016

Authorized officer
Allnutt, Sarah
<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>A</td>
<td>WO 01/30324 A2 (AUFSESS JOACHIM G [AT]) 3 May 2001 (2001-05-03) page 4, paragraph 7 - page 5, paragraph 1; claim 1</td>
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<td>Patent document cited in search report</td>
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