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(54) Title: NANOPARTICULATE BICALUTAMIDE FORMULATIONS

(57) Abstract: The present invention is directed to compositions comprising an acylanilide, such as bicalutamide, having improved solubility in water. The bicalutamide particles of the composition have an effective average particle size of less than about 2000 nm, and are useful in the treatment of prostate cancer.

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NANOPARTICULATE BICALUTAMIDE FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to nanoparticulate compositions comprising an acylanilide, such as but not limited to bicalutamide. The acylanilide particles have an effective average particle size of less than about 2000 nm.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Compositions

Nanoparticulate compositions, first described in United States Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of an acylanilide.

Methods of making nanoparticulate compositions are described in, for example, United States Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" United States Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and United States Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described, for example, in United States Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-

Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate

Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,582,285 for "Apparatus for sanitary wet milling;" 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" 6,811,767 for "Liquid droplet

aerosols of nanoparticulate drugs;" and 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" all of which are specifically incorporated by reference. In addition, United States Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference.

Amorphous small particle compositions are described, for example, in United States Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

B. Background Regarding Bicalutamide

Compositions of the invention comprise an acylanilide, such as bicalutamide. Bicalutamide is commercially available under the registered trademark CASODEX®, marketed by AstraZeneca Pharmaceuticals (Wilmington, Delaware). *The Physicians Desk Reference*, 58th Ed., pp. 3, 306 (2004).

Bicalutamide, also known as propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl] -3-[4-flurophenyl) sulfonyl]-2-hydroxy-2-methyl-, (+ –) is a non-steroidal anti-androgen with no other endocrine activity. Bicalutamide is a fine white to off-white powder offered as a tablet. Bicalutamide is practically insoluble in water at 37° (5 mg per 1000 mL). CASODEX® is a racemate with its anti-androgenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-enantiomer is essentially inactive. *The Physicians Desk Reference*, 58th Ed., p. 658 (2004).

Amide derivatives such as bicalutamide are described in, for example, U.S. Patent No. 4,636,505 to Tucker. U.S. Patent No. 4,636,505 refers to a class of acylanilides.

Bicalutamide is a non-steroidal anti-androgen. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma

is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.

When CASODEX® is combined with luteinizing hormone-releasing hormone (LHRH) analogue therapy, the suppression of serum testosterone inducted by the LHRH analogue is not affected. However, in clinical trials with bicalutamide as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted. *The Physicians Desk Reference*, 58th Ed., p. 658 (2004).

Because conventional bicalutamide tablets are practically insoluble in water at 37°C (5 mg per 1000 mL), bicalutamide tablets have limited bioavailability. This limited bioavailability limits the therapeutic outcome for all treatments requiring bicalutamide. There is a need in the art for bicalutamide formulations which overcome these and other problems associated with conventional bicalutamide.

SUMMARY OF THE INVENTION

The present invention relates to nanoparticulate compositions comprising an acylanalide, such as bicalutamide. The compositions comprise nanoparticulate bicalutamide particles and at least one surface stabilizer adsorbed on or associated with the surface of the bicalutamide particles. The nanoparticulate bicalutamide particles have an effective average particle size of less than about 2000 nm.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate acylanilide, such as bicalutamide nanoparticles, at least one surface stabilizer, a pharmaceutically acceptable carrier, as well as any desired excipients.

Another aspect of the invention is directed to nanoparticulate acylanalide, such as a nanoparticulate bicalutamide composition, having improved pharmacokinetic profiles as compared to conventional bicalutamide formulations.

Another embodiment of the invention is directed to nanoparticulate bicalutamide compositions comprising one or more additional compounds useful in combination therapy

with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of stage D_2 metastatic carcinoma of the prostate.

In another aspect of the invention there is provided a method of preparing the nanoparticulate acylanilide, such as bicalutamide, formulations of the invention. The method comprises: (1) dispersing a acylanilide, such as bicalutamide, in a liquid dispersion medium in which the acylanilide is poorly soluble and dispersible; and (2) mechanically reducing the particle size of the acylanilide, such as bicalutamide, to less than about 2000 nm. At least one surface stabilizer can be added to the dispersion media either before, during, or after particle size reduction of acylanilide. Preferably, the liquid dispersion medium is maintained at a physiologic pH, for example, within the range of from about 3 to about 8, during the size reduction process.

The present invention is also directed to methods of treating a mammal, including a human, using the nanoparticulate acylanilide, such as bicalutamide, formulations of the invention for the for the treatment of prostate cancer, including but not limited to stage D_2 metastatic carcinoma of the prostate. Such methods comprise the step of administering to a subject a therapeutically effective amount of a nanoparticulate acylanilide, such as bicalutamide, formulation of the invention. Also encompassed by the invention is methods of treatment including but not limited to combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of prostate cancer, such as stage D_2 metastatic carcinoma of the prostate using the novel nanoparticulate bicalutamide compositions disclosed herein. Other methods of treatment using the nanoparticulate compositions of the invention are known to those of skill in the art.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

A. Introduction

The present invention is directed to nanoparticulate compositions comprising an acylanilide, preferably bicalutamide. The compositions comprise nanoparticulate bicalutamide particles and preferably at least one surface stabilizer adsorbed on or associated with the surface of the drug. The nanoparticulate acylanilide, preferably bicalutamide, particles have an effective average particle size of less than about 2000 nm.

As taught in the '684 patent, and as exemplified in the examples below, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable, nanoparticulate acylanilide, preferably bicalutamide, formulations can be made.

Advantages of the nanoparticulate acylanilide, preferably bicalutamide, formulations of the invention include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect as compared to conventional forms of bicalutamide; (3) increased bioavailability as compared to conventional microcrystalline forms of bicalutamide; (4) improved pharmacokinetic profiles; (5) improved bioequivalency of the nanoparticulate bicalutamide compositions; (6) an increased rate of dissolution for the nanoparticulate bicalutamide compositions as compared to conventional microcrystalline forms of the same active; (7) bioadhesive bicalutamide compositions; and (8) the nanoparticulate acylanilide, preferably bicalutamide compositions can be used in conjunction with other active agents useful in combination therapy for treating prostate cancer, such as a luteinizing hormone-releasing hormone (LHRH) analogue.

The present invention also includes nanoparticulate acylanilide, preferably bicalutamide compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.,* intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules,

and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

B. Definitions

The present invention is described herein using several definitions, as set forth below and throughout the application.

As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

The term "effective average particle size of less than about 2000 nm", as used herein means that at least 50% of the acylanilide, preferably bicalutamide, particles have a weight average size of less than about 2000 nm, when measured by, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

As used herein with reference to a stable acylanilide, preferably bicalutamide, particle connotes, but is not limited to one or more of the following parameters: (1), acylanilide, preferably bicalutamide, particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the acylanilide, preferably bicalutamide, particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the acylanilide, preferably bicalutamide, particles are chemically stable; and/or (4) where the acylanilide, preferably bicalutamide, has not been subject to a heating step at or above the melting point of the acylanilide, preferably bicalutamide, in the preparation of the nanoparticles of the present invention.

The term "conventional" or "non-nanoparticulate" active agent or acylanilide, such as bicalutamide, shall mean an active agent, such as acylanilide, e.g., bicalutamide,, which is solubilized or which has an effective average particle size of greater than about 2000 nm.

Such non-nanoparticulate agents are also referred to herein as "micronized" agents. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

The phrase "poorly water soluble drugs" as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml.

As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

The term "particulate" as used herein refers to a state of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. The term "multiparticulate" as used herein means a plurality of discrete, or aggregated, particles, pellets, beads, granules or mixture thereof irrespective of their size, shape or morphology.

C. Preferred Characteristics of the Acylanilide Compositions of the Invention

1. Increased Bioavailability

The acylanilide, such as bicalutamide, formulations of the invention are proposed to exhibit increased bioavailability and require smaller doses as compared to prior conventional acylanilide, such as bicalutamide, formulations.

2. Dissolution Profiles

The acylanilide, such as bicalutamide, compositions of the invention are proposed to have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of the acylanilide, such

as bicalutamide, it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

The acylanilide, such as bicalutamide, compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is dissolved. In other embodiments of the invention, at least about 30% or at least about 40% of the acylanilide, such as bicalutamide, composition is dissolved within about 5 minutes. In yet other embodiments of the invention, at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the acylanilide, such as bicalutamide, composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the acylanilide, such as bicalutamide, composition is dissolved within about 20 minutes.

Dissolution is preferably measured in a media which is discriminating. Such a dissolution media will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; *i.e.*, the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

3. Redispersibility Profiles of the Acylanilide Compositions of the Invention

An additional feature of the acylanilide, such as bicalutamide, compositions of the present invention is that the compositions redisperse such that the effective average particle size of the redispersed acylanilide, such as bicalutamide, particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate acylanilide, such as bicalutamide, compositions of the invention did not redisperse to a nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating the acylanilide, such as bicalutamide, into a nanoparticulate particle size. A nanoparticulate size suitable for the present invention is an effective average particle size of less than about 2000 nm.

Indeed, the nanoparticulate active agent compositions of the present invention benefit from the small particle size of the active agent; if the active agent does not redisperse into a

small particle size upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall well below that observed with the liquid dispersion form of the nanoparticulate active agent.

Moreover, the nanoparticulate acylanilide, such as bicalutamide, compositions of the invention exhibit dramatic redispersion of the nanoparticulate acylanilide, such as bicalutamide, particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed acylanilide, such as bicalutamide, particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

Representative electrolyte solutions can be, but are not limited to, HCl solutions,

ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

In other embodiments of the invention, the redispersed acylanilide, such as bicalutamide, particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods. Such methods suitable

for measuring effective average particle size are known to a person of ordinary skill in the art.

Redispersibility can be tested using any suitable means known in the art. *See e.g.,* the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

4. Acylanilide Compositions Used in Conjunction with Other Active Agents

Conventional acylanilide, such as bicalutamide, compositions have limited bioavailability because acylanilide compounds, such as bicalutamide, are practically insoluble in water at 37°C (5 mg per 1000 mL). The present invention is proposed to comprise nanoparticulate acylanilide, such as bicalutamide, compositions to improve the dissolution rate of the poorly soluble active compound. The improvement in dissolution rate is proposed to enhance the bioavailability of acylanilide, such as bicalutamide, allowing a smaller dose to give the same *in vivo* blood levels as larger dosage amounts required with conventional acylanilide, such as bicalutamide, compositions (CASODEX®). In addition, the enhanced dissolution rate is proposed to allow for a larger dose of drug to be absorbed, which increases the efficacy of the acylanilide, such as bicalutamide, and therefore, therapeutic outcome for all treatments requiring an acylanilide, such as bicalutamide. Such treatments include but are not limited to combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of prostate cancer, such as stage D_2 metastatic carcinoma of the prostate.

Another embodiment of the invention is directed to acylanilide, such as bicalutamide, compositions additionally comprising one or more compounds for use in combination therapy which also comprises a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of prostate cancer, such as stage D_2 metastatic carcinoma of the prostate. LHRH analogs are synthetic compounds that are chemically similar to Luteinizing Hormone Releasing Hormone (LHRH), but are sufficiently different that they suppress testicular production of testosterone by binding to the LHRH receptor in the pituitary gland and either have no biological activity and therefore competitively inhibit the action of LHRH, or has

LHRH activity that exhausts the production of LH by the pituitary. LHRH analogues are used in the hormonal treatment of advanced prostate cancer and in the adjuvant and neoadjuvant hormonal treatment of earlier stages of prostate cancer. Examples of such compounds include, but are not limited to, leuprolide acetate (Lupron®) and leuprorelin acetate.

D. Compositions

The present invention provides compositions comprising acylanilide, such as bicalutamide, particles and at least one surface stabilizer. The surface stabilizer is preferably adsorbed on or associated with the surface of the acylanilide, such as bicalutamide, particles. Surface stabilizers especially useful herein preferably physically adhere on, or associate with, the surface of the nanoparticulate acylanilide, such as bicalutamide, particles but do not chemically react with the acylanilide particles or themselves. Individuall molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The present invention also includes acylanilide, such as bicalutamide, compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

1. Acylanilide

The acylanilide of the invention, such as bicalutamide, includes analogs and salts thereof, and can be in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphouse phase, or a mixture thereof. The acylanilide, such as bicalutamide, in the present invention, when applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers.

Examples of acylanilide and derivatives thereof are described, for example, in U.S. 20030045742 A1, for "Methods of synthesizing acylanilides including bicalutamide and derivatives thereof;" U.S. 20050033082 A1 for "Method for producing bicalutamide;" and U.S. Patent No. 6,482,985 for "2-benzyloxy-5-halo-acylanilide compounds and method of

using them," all of which are specifically incorporated by reference.

2. Surface Stabilizers

The present invention is directed to the surprising discovery that stable nanoparticulate acylanilide, such as bicalutamide, compositions can be made. Such stable compositions comprise particles of drug will not agglomerate or adhere to one another.

Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, anionic, cationic, ionic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.,* Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.,* Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of

sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is C18H37CH2(CON(CH3)-CH2(CHOH)4(CH20H)2 (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl □-D-glucopyranoside; n-decyl □-D-maltopyranoside; n-dodecyl □-D-glucopyranoside; n-dodecyl □-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-□-D-glucopyranoside; n-heptyl □-D-thioglucoside; n-hexyl □-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl □-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-□-D-glucopyranoside; octyl □-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate. Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated

alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Nonpolymeric surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium

compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine

dihydrochloride, guanidine hydrochloride, pyridoxine HCl, tolclamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

3. Other Pharmaceutical Excipients

Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Acylanilide

The compositions of the invention contain nanoparticulate acylanilide, such as bicalutamide, particles, which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns), less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than

about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the acylanilide, such as bicalutamide, particles have a particle size of less than the effective average, by weight, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 90%, or at least about 95% of the acylanilide, such as bicalutamide, particles have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, *etc.*

In the present invention, the value for D50 of a nanoparticulate acylanilide, such as bicalutamide, composition is the particle size below which 50% of the acylanilide, such as bicalutamide, particles fall, by weight. Similarly, D90 is the particle size below which 90% of the acylanilide, such as bicalutamide, particles fall, by weight.

5. Concentration of the Acylanilide Derivatives and Surface Stabilizers

The relative amounts of acylanilide, such as bicalutamide, and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the particular acylanilide selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc.*

The concentration of the acylanilide, such as bicalutamide, can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined weight of the acylanilide, such as bicalutamide, and at least one surface stabilizer, not including other excipients.

The concentration of the surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the acylanilide, such as bicalutamide, and at least one surface stabilizer, not including other excipients.

6. Exemplary Nanoparticulate Acylanilide Tablet Formulations

Several potential exemplary acylanilide, such as bicalutamide, tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather

provide exemplary tablet formulations of acylanilide, such as bicalutamide, which can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

Exemplary Nanoparticulate Bicalutamide Tablet Formulation #1

Component	g/Kg
Bicalutamide	about 50 to about 500
Hypromellose, USP	about 10 to about 70
Docusate Sodium, USP	about 1 to about 10
Sucrose, NF	about 100 to about 500
Sodium Lauryl Sulfate, NF	about 1 to about 40
Lactose Monohydrage, NF	about 50 to about 400
Silicified Microcrystalline Cellulose	about 50 to about 300
Crospovidone, NF	about 20 to about 300
Magnesium Stearate, NF	about 0.5 to about 5

Exemplary Nanoparticulate Bicalutamide Tablet Formulation #2

Component	g/KG
Bicalutamide	about 100 to about 300
Hypromellose, USP	about 30 to about 50
Docusate Sodium, USP	about 0.5 to about 10
Sucrose, NF	about 100 to about 300
Sodium Lauryl Sulfate, NF	about 1 to about 30
Lactose Monohydrate, NF	about 100 to about 300
Silicified Microcrystalline Cellulose	about 50 to about 200
Crospovidone, NF	about 50 to about 200
Magnesium Stearate, NF	about 0.5 to about 5

Exemplary Nanoparticulate Bicalutamide Tablet Formulations #3

Component	g/Kg
Bicalutamide	about 200 to about 225
Hypromellose, USP	about 42 to about 46
Ducosate Sodium, USP	about 2 to about 6
Sucrose, NF	about 200 to about 225
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrage, NF	about 200 to about 205
Silicified Microcrystalline Cellulose	about 130 to about 135
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

Exemplary Nanoparticulate Bicalutamide Tablet Formulations #4

Component	g/KG
Bicalutamide	about 119 to about 224
Hypromellose, USP	about 42 to about 46
Ducosate Sodium, USP	about 2 to about 6
Sucrose, NF	about 119 to about 224
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 119 to about 224
Silicified Microcrystalline Cellulose	about 129 to about 134
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

E. Methods of Making Nanoparticulate Acylanilide Compositions

The nanoparticulate acylanilide, such as bicalutamide, compositions can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

The resultant nanoparticulate acylanilide, such as bicalutamide, compositions or dispersions can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations,

lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.*

1. Milling to Obtain Nanoparticulate Acylanilide Compositions

Milling an acylanilide, such as bicalutamide, to obtain a nanoparticulate dispersion comprises dispersing the acylanilide, such as bicalutamide, particles in a liquid dispersion media in which the acylanilide is poorly soluble and dispersible, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the acylanilide, such as bicalutamide, to the desired effective average particle size. The dispersion media can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion media is water.

The acylanilide, such as bicalutamide, particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the acylanilide, such as bicalutamide, particles can be contacted with one or more surface stabilizers before or after attrition. Other compounds, such as a diluent, can be added to the acylanilide/surface stabilizer composition before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

2. Precipitation to Obtain Nanoparticulate Acylanilide Compositions

Another method of forming the desired nanoparticulate acylanilide, such as bicalutamide, compositions is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving bicalutamide in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain Nanoparticulate Acylanilide Compositions

Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing particles of an acylanilide, such as bicalutamide, in a liquid dispersion media, followed by subjecting the dispersion to homogenization to reduce the particle size of the acylanilide, such as bicalutamide, to the desired effective average particle size. The acylanilide, such as bicalutamide, particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the acylanilide, such as bicalutamide, particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the acylanilide/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

F. Methods of Using the Acylanilide Compositions of the Invention

The invention provides a method of rapidly increasing the plasma levels of an acylanilide, such as bicalutamide, in a subject. Such a method comprises orally administering to a subject an effective amount of a composition comprising a nanoparticulate acylanilide, such as nanoparticulate bicalutamide. The acylanilide, such as bicalutamide, composition, in accordance with standard pharmacokinetic practice, produces a maximum blood plasma concentration profile in less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after the initial dose of the composition.

The compositions of the invention are useful in all treatments requiring bicalutamide, including but not limited to, combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of prostate cancer, such as stage D_2 metastatic carcinoma of the prostate.

The acylanilide, such as bicalutamide, compositions of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments

or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms "patient" and "subject" may be used interchangeably.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The nanoparticulate acylanilide, such as bicalutamide, compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the acylanilide, such as bicalutamide, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

"Therapeutically effective amount" as used herein with respect to an acylanilide, such as bicalutamide, shall mean that dosage amount that provides the specific pharmacological response for which the acylanilide, such as bicalutamide is administered in a significant number of subjects. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that acylanilide, such as bicalutamide, dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

One of ordinary skill will appreciate that effective amounts of an acylanilide, such as bicalutamide, can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of an acylanilide, such as bicalutamide, in the nanoparticulate compositions of the invention may be varied to obtain an amount of the acylanilide, such as bicalutamide, that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic

effect, the route of administration, the potency of the administered acylanilide, such as bicalutamide,, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

EXAMPLES

Example 1

The purpose of this example was to demonstrate how a nanoparticulate bicalutamide could be made.

An aqueous dispersion of 10% (w/w) bicalutamide, combined with 2% (w/w) hypromellose and 0.05% (w/w) dioctylsulfosuccinate (DOSS), could be milled in a 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see e.g., U.S. Patent No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical) (89% media load). An exemplary milling speed that could be used is 2500 rpms, and an exemplary time period for milling that could be used is 60 minutes.

Following milling, the particle size of the milled bicalutamide particles could be measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The desired effective average particle size of the bicaluatamide particles is less than about 2000 nm.

* * * *

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover

the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

We claim:

1. A stable nanoparticulate acylanilide composition comprising:
   (a) bicalutamide particles having an effective average particle size of less than about 2000 nm; and
   (b) at least one surface stabilizer.

2. The composition of claim 1, wherein the bicalutamide is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

3. The composition of claim 1 or claim 2, wherein the effective average particle size of the bicalutamide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

4. The composition of any one of claims 1 to 3, wherein:
(a) the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration;
(b) the composition is a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, tablets, capsules, and granules;
(c) the composition is a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or
(d) any combination of (a), (b), or (c).

5. The composition of any one of claims 1 to 4, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition of any one of claims 1 to 5, wherein:

(a) the bicalutamide is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the bicalutamide and at least one surface stabilizer, not including other excipients;

(b) the surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the bicalutamide and at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

7. The composition of any one of claims 1 to 6, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

8. The composition of any one of claims 1 to 7, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

9. The composition of any one of claims 1 to 8, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters,

polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic non-polymeric compound, a cationic phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-

alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

10. The composition of any one of claims 1 to 9, additionally comprising one or more non-bicalutamide active agents.

11. The composition of claim 10, wherein the non-bicalutamide active agent is a luteinizing hormone-releasing hormone (LHRH) analogue.

12. The composition of any one of claims 1 to 11, wherein upon administration to a mammal the bicalutamide particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600

nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

13. The composition of any one of claims 1 to 12, wherein the composition redisperses in a biorelevant media such that the bicalutamide particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

14. The composition of claim 13, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

15. Use of the composition of any one of claims 1 to 14 for the manufacture of a medicament.

16. The use of claim 15, wherein the medicament is useful in treating prostate cancer.

17. The use of claim 16, wherein the prostate cancer is stage D_2 metastatic

carcinoma of the prostate.

18. A method of making a bicalutamide composition comprising contacting particles of bicalutamide with at least one surface stabilizer for a time and under conditions sufficient to provide a bicalutamide composition having an effective average particle size of less than about 2000 nm.

19. The method of claim 18, wherein the contacting comprises grinding, wet grinding, homogenizing, or precipitation.

20. The method of claim 18, wherein the effective average particle size of the bicalutamide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

INTERNATIONAL SEARCH REPORT

al application No
:2005/046257

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/277 A61K9/14 A61P35/00

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 data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, PASCAL, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/013472 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HEDBERG, PIA, MARGARETHA, CECI) 20 February 2003 (2003-02-20) claims; example 4	1-20
X	WO 2004/009057 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; SKANTZE, TOMMY, URBAN; LINDFOR) 29 January 2004 (2004-01-29) claims; example 4	1-20
X	US 2002/110597 A1 (RYDE NIELS P ET AL) 15 August 2002 (2002-08-15) abstract	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2006	16/05/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zimmer, B

INTERNATIONAL SEARCH REPORT

International application No
5/046257

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant	
X	TYRRELL C J: "CASODEX: A PURE NON-STEROIDAL ANTI-ANDROGEN USED AS MONOTHERAPY IN ADVANCED PROSTATE CANCER" PROSTATE, WILEY-LISS, NEW YORK, NY, US, vol. 4, 1992, pages 97-104, XP000908815 ISSN: 0270-4137 page 97	15-17
X	WO 2004/006959 A (ELAN PHARMA INTERNATIONAL, LTD; BOSCH, H., WILLIAM; HILBORN, MATTHEW,) 22 January 2004 (2004-01-22) the whole document	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

ional application No
US2005/046257

Patent document cited in search report		Publication date		Patent family	Publication
WO 03013472	A	20-02-2003	BR	0211705 A	28-09-2004
			CA	2456180 A1	20-02-2003
			CN	1564677 A	12-01-2005
			EP	1416917 A1	12-05-2004
			JP	2005500362 T	06-01-2005
			MX	PA04001071 A	20-05-2004
			NZ	530916 A	29-07-2005
			US	2005009908 A1	13-01-2005
WO 2004009057	A	29-01-2004	AU	2003244871 A1	09-02-2004
			BR	0312631 A	19-04-2005
			CA	2492709 A1	29-01-2004
			CN	1668280 A	14-09-2005
			EP	1524964 A1	27-04-2005
			JP	2006504511 T	09-02-2006
			MX	PA05000595 A	19-04-2005
			US	2005202092 A1	15-09-2005
			ZA	200410343 A	17-10-2005
US 2002110597	A1	15-08-2002	AU	9501701 A	02-04-2002
			CA	2416109 A1	28-03-2002
			EP	1318788 A1	18-06-2003
			JP	2004513886 T	13-05-2004
			WO	0224163 A1	28-03-2002
			US	6375986 B1	23-04-2002
WO 2004006959	A	22-01-2004	AU	2003261167 A1	02-02-2004
			CA	2492488 A1	22-01-2004
			EP	1551457 A1	13-07-2005
			JP	2005536512 T	02-12-2005