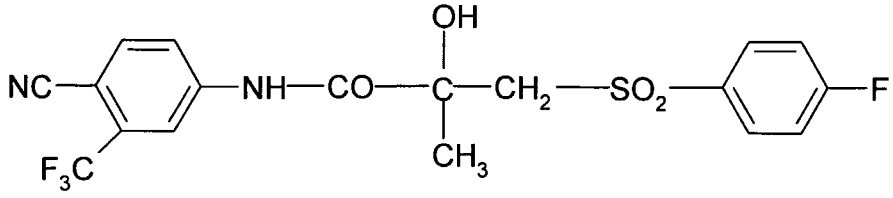
PHARMACEUTICAL FORMULATION COMPRISING (R)-BICALUTAMIDE

The present invention relates to a pharmaceutical formulation comprising an enteric polymer having a pK_a from 3 to 6 and 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer. The invention also relates to a daily pharmaceutical dose of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide provided by such a formulation. In addition, the invention relates to the use of such an enteric polymer in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide for increasing the bioavailability of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide; for reducing inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide; or for treating and/or reducing the risk of prostate cancer in a patient.

BACKGROUND TO THE INVENTION

Bicalutamide, a non-steroidal anti-androgen, is the racemate of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and is known by the AstraZeneca trade name CASODEX™. EP-100172 discloses 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide (named in EP-100172 as 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)aniline) as the 8th compound listed in the table in Example 6. The corresponding structure is shown in formula I:-



I

Bicalutamide can be used to combat prostate cancer. The properties and usefulness of bicalutamide as an anti-androgen have been reviewed in B J A Furr *et al.*, Urology, 1996, 47 (Suppl. 1A), 13-25, and G J C Kolvenbag *et al.*, Urology, 1996, 47 (Suppl. 1A), 70-79. 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide can exist in distinct R- and S- enantiomeric forms. The R-enantiomer is the (-) isomer and is the pharmacologically active compound *in vivo*. For further details of the enantiomers, reference is made to Tucker and Chesterton, *J. Med. Chem.* 31, pp 885-887 (1988).

The chemical synthesis of racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is described in US4636505, and this disclosure is incorporated herein by reference. The R-enantiomer may be obtained by the resolution of enantiomers from the racemate or resolution of precursors of the enantiomers using fractional crystallisation or chromatographic separation of diastereomeric esters of chiral acids. Other methods will, however, be evident to the skilled addressee using routine techniques for the preparation of enantiomers. For example, the R-enantiomer may be prepared by simple crystallisation and chromatographic resolution (see, for example, Wilen and Lochmuller, "Tables of Resolving Agents", *J. Chromatography*, 113, 283-302 (1975) and E L Eliel, *Stereochemistry of Carbon Compounds*, McGraw Hill (1962)). Another method involves resolution of the carboxylic acid precursor, 3-(4-fluorophenyl)-2-hydroxy-2-methylpropanoic acid, by fractional crystallisation of diastereomeric salts with chiral amines. The Tucker and Chesterton reference cited above discloses the chromatographic separation of the R-and S- enantiomers from racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide. The method involves the chromatographic separation of R-camphanoyl esters of the racemate and their hydrolysis and oxidation to the R- and S-enantiomers. This disclosure is incorporated herein by reference specifically to provide an illustration of a method of obtaining the enantiomers for use in the present invention.

Bicalutamide (4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide racemate) is used in conventional oral tablet form (eg, at a daily monotherapy dose of 150mg) to combat prostate cancer in men. The bioavailability of the bicalutamide to the patient is determined to a certain extent by the dissolution rate and solubility of the drug in the GI tract, which affects absorption across mucosal membranes in the GI tract. The relative bioavailability of bicalutamide for a series of formulations can be

assessed by determining the area under the curve (AUC) of a graph of plasma bicalutamide concentration *v.* time elapsed since administration of the bicalutamide. As a consequence of sub-optimal rates of dissolution and degree of solubility of the drug, there is observed a high degree of inter-patient variability in the bioavailability of bicalutamide administered in conventional tablet form. This may result in sub-optimal treatment efficacy in a proportion of patients. In addition, the maximum systemic exposure achievable after dosing the conventional tablet is limited, such that at conventional tablet doses in excess of 150mg, there is a significant reduction in bicalutamide bioavailability. At conventional tablet doses above 300mg, no further significant increase in systemic exposure is achievable

It would be desirable to extend the therapeutic potential of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide by increasing the bioavailability of the drug and/or reducing inter-patient variability in plasma concentrations of bicalutamide, relative to conventional bicalutamide, as a result of reduced inter-patient variability in the absorption of the drug.

Such increased bioavailability could be useful in enabling a reduction in the daily dose of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide required to achieve the same level of bioavailability seen with a conventional formulation.

A possible benefit of achieving relatively higher bioavailability, relative to conventional bicalutamide, could also be the ability to extend treatment to more advanced stages of prostate cancer than are currently treated with the conventional formulations. This could be useful, for example, for treating patients with metastatic prostate cancer, using for example 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide as a monotherapy (ie, not in combination with LHRH analogue therapy or surgical castration).

As another advantage, it would also be desirable to reduce inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide as a result of reduced inter-patient variability in the absorption of bicalutamide. This would increase predictability of the treatment and increase uniformity of treatment in a patient population.

It would also be desirable to provide a 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide formulation having good storage stability.

EP-0988863 deals with the issue of increasing the bioavailability of poorly soluble drugs in general. 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is not specifically addressed. The disclosed solution is to provide a formulation comprising a water-insoluble complex of the drug and a water-insoluble ionic polymer. No specific class of polymer is required, and the polymer can be cationic or anionic, but must have a molecular weight greater than about 80,000 D and a glass transition temperature equal or greater than about 50°C.

EP-1027886 also deals with the issue of increasing the bioavailability of poorly soluble drugs in general. Again, 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is not specifically addressed. The disclosed solution is to provide a solid dispersion formulation comprising a low-solubility drug and a polymer. The latter can be one of many possible polymers, as long as it has a glass transition temperature of at least 100°C measured at 50% relative humidity. Some enteric polymers (eg, HPMCP polymers, including grades HP-50™, HP-55™ and HP-55S™) are explicitly excluded from use, since it is explained that all of these polymers absorb sufficient water upon equilibration at 50% relative humidity that their respective glass transition temperatures drop below 100°C. Hydroxypropyl methylcellulose acetate succinate (HPMCAS), another enteric polymer, is also excluded when used alone.

The present invention aims to improve upon the conventional formulation of bicalutamide (racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) by increasing the therapeutic potential of bicalutamide as discussed above.

The present invention aims to provide a 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide formulation having enhanced storage stability.

SUMMARY OF THE INVENTION

The present invention fulfils this aim by providing a pharmaceutical formulation for administration to a patient, the formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is

provided in the form of the R-enantiomer. It is contemplated that one or a mixture of such enteric polymers can be used.

The invention also provides a daily pharmaceutical dose of 5 to 1000 mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide administrable to a patient for treating and/or reducing the risk of prostate cancer in the patient, wherein the dose comprises 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer. In one embodiment the dose is from 25 to 600mg.

Further aspects of the invention relate to the use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a medicament mucosally administrable to a patient, for

(a) increasing the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the patient; or

(b) treating and/or reducing the risk of prostate cancer in the patient. As explained below, reducing the risk of prostate cancer includes reducing the risk of re-occurrence of prostate cancer.

In addition, the invention relates to the use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a medicament mucosally administrable to patients, for reducing inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

Furthermore, the invention relates to the use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-

(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a pharmaceutical formulation, for enhancing the storage stability, of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the formulation, relative to non-solid dispersion formulations of bicalutamide.

Another aspect of the invention relates to the use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a pharmaceutical formulation mucosally administrable to a patient, for enhancing the storage stability of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the formulation in addition to increasing the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the patient and/or reducing inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, relative to conventional bicalutamide formulations or non-solid dispersion formulations of bicalutamide.

FIGURES

Fig. 1 Dissolution of bicalutamide (ie, racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) from various solid dispersion formulations comprising enteric polymers (50mg bicalutamide in 900ml of media).

Key:-

Circles - conventional bicalutamide tablet formulation

Broken line- HPMCP HP-55S

Diamonds - EUDRAGIT™ L100

Squares - HPMCAS AQOAT™ LG

Fig. 2 Dissolution of bicalutamide from various solid dispersion formulations comprising enteric or non-enteric polymers (50mg bicalutamide in 900ml of media).

Key:-

Diamonds - HPMC PHARMACOAT™ 606

Squares - METOLOSE™ 60SH 50cp

Triangles - PEG4000

Crosses - PLA:PEG [2kDa:2kDa]

Broken line- HPMCP HP-55S

Circles - conventional bicalutamide tablet formulation

Fig. 3 Dissolution of bicalutamide from solid dispersion formulations (50mg bicalutamide in 900ml of media) comprising bicalutamide with HP-55S at various weight ratios.

Key:-

The following ratios relate to weight ratios of bicalutamide:HP-55S

Diamonds - 1:5

Squares - 1:4

Triangles - 1:3

Crosses - 1:2

Circles - 1:1

Broken line - conventional bicalutamide tablet formulation.

Fig. 4 Plasma profiles following administration of bicalutamide formulations to dogs (n=6, 450mg bicalutamide dose). The vertical bars indicate variability.

Key:-

Solid line - solid dispersion of 1:3 by weight of bicalutamide:HP-55S

Broken line- conventional bicalutamide tablet formulation.

Fig. 5 Dissolution of bicalutamide (ie, racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) and optically pure R-4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) from solid dispersion formulations (50mg 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in 900ml of media, 1:3 drug : polymer ratio).

Key:-

Triangles - conventional bicalutamide tablet formulation

Diamonds - bicalutamide solid dispersion

Squares - R-4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide solid dispersion

Fig. 6 Dissolution of bicalutamide (ie, racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) and optically pure R-4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) from solid dispersion formulations (50mg 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in 900ml of media, 1:1 drug : polymer ratio).

Key:-

Triangles - conventional bicalutamide tablet formulation

Diamonds - bicalutamide solid dispersion

Squares - R-4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide solid dispersion

DETAILED DESCRIPTION OF THE INVENTION

The inventors chose to investigate solid dispersion formulations as a possible means of fulfilling at least one of the aims stated above. In terms of the aim of increasing the therapeutic potential of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, the inventors sought to increase the therapeutic potential by achieving one or both of an increase the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and a decrease in inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide relative to conventional bicalutamide.

The prior art teaches a very wide range of possible polymers for solid dispersion, in order to increase the bioavailability of drugs in general. The inventors have now surprisingly found that the therapeutic potential of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide can be increased by formulating 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion specifically with an enteric polymer having

a pK_a from 3 to 6, wherein >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer. As the non-limiting example section below demonstrates, such an increase in therapeutic potential for 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is not achieved with other polymers.

Thus, according to one aspect of the invention there is provided a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

Various materials have conventionally been used to coat pharmaceutical tablets, capsules and granules to be compressed into tablets or used to fill capsules. Reference is made to Schroeter, L C, Coating of Tablets, Capsules and Pills, Remington's Pharmaceutical Sciences, 13th ed., 1965, p. 604, which reviews more than 60 enteric coating materials. These include coating materials (eg, carnauba wax, stearic acid and paraffin) that rely on erosion in the intestinal tract, and enteric polymers that are designed to resist the destructive action of gastric fluid and to disintegrate in the intestinal tract. Enteric polymers are thus by definition pH-sensitive and have ionisable acid groups. The acid groups are nonionized and therefore poorly soluble in water. Ionisation, and thus increased solubility, occurs in the intestinal tract, so that the polymers are substantially insoluble in the low pH environment of the gastric fluid (pH 1 to 3.5), but rapidly dissolve at the pH of intestinal fluid, so that, as the dosage form empties into the duodenum a dramatic change in pH occurs, leading to ionisation of the acid groups and increased solubility. The particular enteric polymers used in the present invention are those enteric polymers that have a pK_a from 3 to 6. In one example, the lower end of this range is 3.5, 4 or 4.5. In one example, the upper end of the range is 5 or 5.5.

As the skilled addressee knows, the Henderson-Hasselbach equation may be used to determine the pK_a according to the following equation:-

$$pK_a = pH - \log(\text{concentration of non-ionised polymer} \div \text{concentration of ionised polymer})$$

At a pH two units below the pK_a, only approximately 1% of the acid groups will be ionised, and the polymer will be poorly soluble in gastric fluid. As the pH increases, the

percentage of ionised acid groups increases, such that when the pH exceeds the pK_a by two units the percentage of ionised groups is approximately 100%, and the polymer will be soluble in the intestines.

In one embodiment, the enteric polymer is selected from hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxpropyl methylcellulose acetate pthalate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose succinate, a methacrylic acid copolymer, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), methylcellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), cellulose proprionate pthalate, hydroxypropyl cellulose butyrate pthalate, hydroxypropyl cellulose acetate pthalate succinate, hydroxypropyl methylcellulose trimellitate, cellulose acetate trimellitate (CAT), methylcellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose proprionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terepthalate and cellulose acetate isopthalate.

The use of the term "hydroxypropyl methylcellulose phthalate polymer", or HPMCP, is known to the skilled reader for classifying a group of polymers which share the same basic structural features and include such polymers as: hypromellose phthalate; methylhydroxypropylcellulosi pthalas; cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl; as well as commercially available polymers HP-55™, HP-55S™ and HP-50™ (available from Shin-Etsu Chemical Industry Co., Ltd., Japan or appointed distributors).

Preferably the hydroxypropylmethylcellulose phthalate polymer has a molecular weight (Mw) from 20kDa to 200kDa, eg from 80kDa to 130kDa. In one embodiment, the Mw is less than 150kDa, or less than 100kDa. HP-50, HP-55 and HP-55S are examples of hydroxypropylmethylcellulose phthalate polymers. HP-55 has a Mw 84kDa. HP-55S has a Mw of 132kDa. HP-50 has a Mw 78kDa. HP-50 is soluble at pH≥5, whereas HP-55 and HP-55S are soluble at pH≥5.5. In one embodiment, the bicalutamide is in a solid dispersion with at least one polymer selected from HP-50, HP-55 and HP-55S. Thus, it is contemplated that a mixture of two or more of these HPMCP polymers can be used.

HPMCAS (trade name: AQOAT, available from Shin-Etsu Chemical Industry Co., Ltd., Japan or appointed distributors) is available in the following grades: AS-LF, AS-MF, AS-HF, AS-LG, AS-MG and AS-HG. The AS-L grades are soluble at pH ≥5.5, the AS-M grades are soluble at pH≥ 6.0 and the AS-H grades are soluble at pH≥ 6.5. In one embodiment, the bicalutamide is in a solid dispersion with at least one polymer selected from HPMCAS grades AS-L, AS-M, AS-H. Thus, it is contemplated that a mixture of two or more of these HPMCAS polymers can be used.

Methacrylic acid copolymer is a fully polymerised copolymer of methacrylic acid and methacrylic acid methyl ester. Grade A (trade name: EUDRAGIT™ L 100, available from Rohm Pharma or appointed distributors) and grade B (trade name EUDRAGIT™ S 100) are available. The grades differ in the ratio of free carboxyl groups to ester groups and, therefore, differ in solubility profiles. Type A has a ratio of approximately 1:1 and is soluble at pH≥6. Type B has a ratio of approximately 1:2 and is soluble at pH≥7. Another grade (EUDRAGIT™ L 30 D-55) is soluble at pH≥5.5. In one embodiment, the bicalutamide is in a solid dispersion with at least one methacrylic acid copolymer. Thus, it is contemplated that a mixture of two or more of these polymers (eg, grades A and B) can be used.

PVAP is soluble at pH≥5 and is available from Colorcon Inc or appointed distributors.

CAP (available from FMC Corporation as part of a powdered product, AQUATERIC™) solubilises at pH≥6.5.

CAT is available from Eastman Fine chemicals, Zurich, Switzerland.

In one particular embodiment there is provided a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with HP-55S enteric polymer, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

The term "solid dispersion" is a well-known term in the art, which refers to a dispersion of one or more active ingredients in an inert carrier or matrix at solid state, typically, but not exclusively, prepared by conventional melting (fusion), solvent, or melting-solvent methods. Terms also used to describe this type of approach are solid solutions, coevaporates and coprecipitates (W.L. Chiou and S. Riegelman, "Applications of Solid

Dispersion Systems", J. Pharm. Sci. **60**:1281-1302, 1971). In one embodiment the dispersion is manufactured by melt extrusion.

A preferred ratio of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide: enteric polymer by weight is from 1:0.25 to 1:10. More preferably the lower limit of this range is 1:0.5, 1:0.75 or 1:1. Preferably, the upper limit of this range is 1:<3, 1:3 or 1:5. Examples of ranges of ratios are 1:1 to 1:3 or 1:0.25 to 1:<3.

One aspect of the invention provides a pharmaceutical dose of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, comprising from 25 to 600 mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer. Another provides a daily (once a day) pharmaceutical dose of 25 to 600mg 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide administrable to a patient for treating and/or reducing the risk of prostate cancer in the patient, wherein the dose comprises 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6 and >50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer. Preferably, the dose has an upper limit of 1000, 500, 450, 400, 300, 200, 150, 125, 100, 75 or 50mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide. Examples of other ranges include: 5 to 1000mg, 25 to 600mg and 25 to 450mg. In one example, the dose of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is 450mg.

The daily, once a day, dose is preferably provided in a single unit format, e.g. tablet or capsule. However, multiple dose units (i.e. 1, 2, 3 etc.) are also encompassed.

Additional excipients may be included in the formulation or dose. For example, the formulation or dose may comprise one or more fillers, binder, disintegrants and/or lubricants.

Suitable fillers include, for example, lactose, sugar, starches, modified starches, mannitol, sorbitol, inorganic salts, cellulose derivatives (e.g. microcrystalline cellulose, cellulose), calcium sulphate, xylitol and lactitol.

Suitable binders include, for example, polyvinylpyrrolidone, lactose, starches, modified starches, sugars, gum acacia, gum tragacanth, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, copolyvidone, gelatin and sodium alginate.

Suitable disintegrants include, for example, crosscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycollate, corn starch, microcrystalline cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

Suitable lubricants include, for example, magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols and sodium stearyl fumarate.

Additional conventional excipients which may be added include preservatives, stabilisers, anti-oxidants, silica flow conditioners, antiadherents or glidants.

Other suitable fillers, binders, disintegrants, lubricants and additional excipients which may be used are described in the Handbook of Pharmaceutical Excipients, 3rd Edition; The Theory and Practice of Industrial Pharmacy, 3rd Edition 1986; Pharmaceutical Dosage Forms 1998; Modern Pharmaceutics, 3rd Edition 1995; Remington's Pharmaceutical Sciences 20th Edition 2000.

Preferably, the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide will be present in an amount of 1 to 80% , and preferably from 1 to 50% (more preferably 2 to 25% or 2 to 15%) by weight of the solid dispersion.

Preferably, one or more fillers will be present in an amount of 1 to 70% by weight of the formulation or dose.

Preferably, one or more binders will be present in an amount of 2 to 40% by weight of the formulation or dose.

Preferably, one or more disintegrants will be present in an amount of 0.5% to 25%, and especially 4 to 10% by weight of the formulation or dose.

It will be appreciated that a particular excipient may act as both a binder and a filler, or as a binder, a filler and a disintegrant. Typically the combined amount of filler, binder and disintegrant comprises, for example, 1 to 90% by weight of the formulation or dose.

Preferably, one or more lubricants will be present in an amount of 0.25 to 5%, and especially 1 to 2% by weight of the formulation or dose.

Preferably, one or more wetting agents will be present in the solid dispersion in an amount of 0.1 to 5% (more preferably, 1 to 2%) by weight of the solid dispersion. The presence of a wetting agent provides a further enhancement of the increase in therapeutic potential achieved with the present invention. Examples of suitable wetting agents include sodium dodecyl sulphate (sodium lauryl sulphate); docusate sodium; polyoxyethylen sorbitan fatty acid esters, eg polysorbates 20, 40, 60 and 80; polyoxyethylene castor oil derivatives, eg Cremophor RH40™; and poloxamers.

Methods for preparing solid dispersions are known in the art and typically comprise the steps of dissolving the drug and the polymer in a common solvent and evaporating the solvent. The solvent can be routinely selected according to the polymer used and the preparation method. Examples of solvents are: acetone, acetone/dichloromethane, methanol/dichloromethane, acetone/water, acetone/ethanol, dichloromethane/ethanol or ethanol/water. For HP-50, for example, the last four solvents can be used. For HPMCAS, for example, acetone, methanol, ethanol/water and methylene chloride/ethanol can be used. For methacrylic acid copolymers, isopropyl alcohol can be used. For polyvinyl acetate phthalate, for example, methanol, ethanol, acetone/methanol, acetone/ethanol and methanol/methylene chloride can be used. For CAP, for example, ether/alcohols, ketones (eg, acetone), esters and cyclic ethers can be used. Methods for evaporating solvent include rotary evaporation, spray drying, lyophilisation and thin film evaporation. Other techniques may be used such as solvent controlled precipitation, pH controlled precipitation, spray congealing and supercritical fluid technology.

When referring to a solid dispersion we do not exclude the possibility that a proportion of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide may be dissolved within the polymer used, the exact proportion, if any, will depend upon the particular enteric polymer(s) selected.

In one embodiment of the formulation or dose, ≥60%, ≥70%, ≥80%, ≥85%, ≥90%, ≥95%, ≥98% or ≥99% or thereabout of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer. In a preferred embodiment, 100% or substantially 100% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is

provided in the form of the R-enantiomer. By "substantially 100%" we mean that the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided as the pure R-enantiomer, or there is a trace (<1%) of the S-enantiomer present. As the experimental section below shows, the predominance of the R-enantiomer in the present invention provides for a 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide formulation with good storage stability and an enhanced therapeutic potential.

In the formulations of the invention, at least some of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide may be present in amorphous form in the solid dispersion with the enteric polymer. The provision of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in amorphous form is additionally advantageous, since it further increases the solubility and dissolution rate of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, thereby enhancing the increase in therapeutic potential achieved with the present invention. Whether or not drug is present in amorphous form can be determined by conventional thermal analysis or X-ray diffraction. In one embodiment, at least 25% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the formulation is present in amorphous form. More preferably, this amount is at least 30%, 40%, 50%, 75%, 90%, 95% or 99%. The most preferred embodiment is where 100% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the formulation is in amorphous form. The amorphous form applies to the bicalutamide drug as a whole, thus the proportion of amorphous drug can be S-enantiomer or R-enantiomer or both.

In another aspect of the invention there is provided a solid dispersion of an enteric polymer having a pK_a from 3 to 6 with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

The formulations and doses are mucosally administrable, ie administrable to mucosal membranes for absorption across the membranes. To this end, suitable routes of administration include administration by inhalation, as well as oral, intranasal and rectal administration. Oral administration is particularly preferred. A tablet or other form of the

formulation would be chosen by the skilled addressee according to the route of administration.

The 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is useful to provide an anti-androgenic effect, in that this compound blocks androgen activity in a patient. The anti-androgenic effect is useful for treating cancer, for example prostate cancer. Particular examples are advanced prostate cancer and early prostate cancer. The anti-androgenic effect may be useful for prophylaxis, in order to reduce the risk of prostate cancer occurrence in patients or re-occurrence (eg, following prostatectomy or radiation therapy aimed at curing the patient). This could be especially useful in men genetically pre-disposed to prostate cancer. Conventional methods are available to classify patients according to their risk of contracting prostate cancer, for example by assessment of family history and measurements over time of particular blood proteins such as prostate specific antigen (PSA). Other uses for the anti-androgenic effect are the treatment of a non-malignant disease of the prostate gland (eg, benign prostatic hyperplasia or hypertrophy), testotoxicosis, hirsutism and acne. These conditions, in conjunction with prostate cancer, will be referred to herein as prostatic disorders.

The patient can be a human male, eg an adult, but the treatment of other mammals is also contemplated.

Thus, according to a further aspect of the invention there is provided a method for treating prostate cancer and/or reducing the risk of prostate cancer in a patient comprising administering to a patient in need thereof of a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

According to another aspect there is provided a method for treating prostate cancer and/or reducing the risk of prostate cancer in a patient comprising administering to a patient in need thereof of a pharmaceutical dose of 5 to 1000 mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein the dose comprises 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-

fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

Each of these treatment methods for prostate cancer can also be applied to the prostatic disorders generally.

Further aspects of the invention include:

A method for increasing the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a patient comprising administration to the patient an effective amount of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer. In one embodiment of this aspect of the invention, at least 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is present in the solid dispersion in amorphous form

A method for enhancing the storage stability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein at least 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in amorphous form, comprising use of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide wherein greater than 50% is in the form of the R-enantiomer.

A method for preparing a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide with reduced inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and/or increased bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the patient comprising forming a solid dispersion of an enteric polymer having a pK_a from 3 to 6 with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

Each of these aspects of increased bioavailability, enhanced storage stability and reduced interpatient variability are relative to the same bioequivalent dose of conventional bicalutamide.

Use of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a medicament for treating prostate cancer and/or reducing the risk of prostate cancer in the patient.

Use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a medicament with reduced inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, relative to conventional bicalutamide formulations, for patients in need of treatment with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

Use of greater than 50% of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the form of the R-enantiomer in the manufacture of a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6.

Use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a pharmaceutical formulation mucosally administrable to a patient, for enhancing the storage stability of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the formulation in addition to increasing the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-

fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the patient and/or reducing inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

The invention will be further described with reference to the following non-limiting examples:

EXPERIMENTAL

A: Comparative Examples

The following examples are not according to the present invention, but are included to provide a suitable context for the interpretation of the examples according to the present invention (see section B).

In Vitro Assessment of Various Solid Dispersion Formulations

The inventors formulated a solid dispersion of bicalutamide (racemic a 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) with representative enteric polymers having a pK_a in the range of 3 to 6 (in this case HPMCP HP-55S, EUDRAGIT L100 and HPMCAS AQOAT LG) and compared these against a conventional bicalutamide tablet formulation and also (using HPMCP HP-55S as a representative enteric polymer) against solid dispersions using several different non-enteric polymers (polyethylene glycol (PEG) 4000, PLA:PEG [2kDa:2kDa] (polylactide:methoxypolyethylene glycol [2kDa:2kDa]), hydroxypropyl methylcellulose (HPMC) PHARMACOAT™ 606 and METOLOSE 60SH 50cp) with bicalutamide. Each formulation had a weight ratio of bicalutamide:polymer of 1:5. The formulations were assessed for an improvement in therapeutic potential using an *in vitro* dissolution test.

The performance of solid dispersions having varying weight ratios of bicalutamide:HP-55S was also assessed.

Preparation of Solid Dispersion Formulations

Solid dispersions having a 1:5 ratio by weight of bicalutamide:polymer were prepared as follows.

0.5g of bicalutamide and 2.5g of polymer were weighed directly into a 250ml round bottom flask and dissolved in 80ml of acetone:dichloromethane (3:1). The solvent was removed on a rotary evaporator or by spray drying. The formulation was placed in a vacuum oven and dried under high vacuum at 40°C for 24 hours.

The formulation was retrieved from the flask and dry milled using a Fritsch mill. The formulation was then dried for a further 24 hours under high vacuum at 40°C.

In order to produce formulations having ratios other than 1:5, weights and volumes in the process should be adjusted so that they are pro-rata to those described above.

In vitro Dissolution Test

(a) Solid Dispersion with Enteric Polymers *v.* Solid Dispersion With Non-Enteric Polymers

The formulations were weighed into hard gelatin capsules (equivalent to 50mg drug) and dissoluted in 900ml media [either 0.25% sodium dodecyl sulphate solution or pH6.5 buffer] for one hour at 37°C (paddle speed 75rpm). 5ml samples were then removed with a plastic syringe at 5, 10, 20, 30, 45 and 60 minutes. Each sample was centrifuged (14,000rpm) at ambient temperature for 15 minutes and then analysed by HPLC using the following conditions:-

Eluent:	58% ACN/42% water/0.2% formic acid
Column:	15cm Luna 5um, 3mm id column (with guard)
Detection wavelength:	270nm
Flow rate:	1ml/min
Temperature:	ambient
Injection:	10ul
Retention time:	approximately 2 minutes

Figures 1 and 2 show the results of *in vitro* dissolution tests performed on the various solid dispersions. As Fig. 1 shows, 100% of bicalutamide in solution was achieved with the HPMCP HP-55S, EUDRAGIT L100 and HPMCAS AQOAT LG solid dispersions and supersaturation was maintained over the 60 minute test (ie, no drug precipitation was observed), which is a significant improvement over the conventional tablet. Compare this against the results (Fig. 2) for the PLA:PEG solid dispersion, which did not show any improvement over the conventional tablet formulation. The PEG4000 solid dispersion also was much inferior to the formulations using enteric polymers (Fig. 2), the former achieving only just over 40% of bicalutamide in solution. In addition, reference to Fig. 2 shows that the solid dispersions with METOLOSE 60SH 50cp and HPMC PHARMACOAT 606 only achieved approximately 58% and 70% of bicalutamide in solution.

(b) Solid Dispersions With Varying Ratios of Bicalutamide:HP-55S

Solid dispersions were made with weight ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 bicalutamide:HP-55S. These were tested in the *in vitro* dissolution test, and the results are presented in Fig. 3. A conventional bicalutamide tablet formulation was included for comparison.

As Fig. 3 shows, for all of the formulations comprising HP-55S, 100% of bicalutamide in solution was achieved and supersaturation was maintained over the 60 minute test. These results were superior to the results achieved with the conventional formulation.

In Vivo Evaluation

Oral doses of bicalutamide were administered to fasted dogs (equivalent to 450mg drug)(n=6). The formulations dosed were conventional CASODEX™ tablets and a 1:3 [bicalutamide:HP55S] solid dispersion. The solid dispersion was prepared as described earlier, however the solvent was removed by spray drying as opposed to rotary evaporation. Each oral dose was followed by 20ml of water. Blood samples were taken pre-dose and post dose at 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, 72, 96, 120, 144, 168 hours. The samples centrifuged at 3000rpm for 15 minutes, the plasma removed into plain blood tubes and stored at -20°C until analysis. Samples were analysed by using a suitable extraction method followed by LC-MS.

Summary of Pharmacokinetic Parameters

FORMULATION	Cpmax (μg/ml)	Tmax (hours)	AUC (μg/h/ml)*
HP-55S solid dispersion	13	30	1504 ± 309
Conventional formulation	5	30	500 ± 405

* AUC from 0 to 144 hours

These data, as well as Fig. 4, show that the bioavailability of bicalutamide is greater with the solid dispersion using the enteric HP-55S polymer. In fact, the AUC measurements show a figure for the HP-55S solid dispersion that is almost 3 times that of the conventional tablet formulation. In addition, C_{max} for the HP-55S solid dispersion is almost 3 times that of the conventional tablet formulation. Furthermore, inter-subject variability in the plasma levels of bicalutamide is lower with the HP-55S solid dispersion than with the conventional tablet formulation (for variability/total AUC, compare a figure of 309/1504 μg/h/ml for theHP-55S solid dispersion against a figure of 405/500 μg/h/ml for the conventional tablet

formulation). Formulations according to the present invention display similar imporovements over a conventional tablet formulation.

B: Examples in accordance with the invention

Enhancement of therapeutic potential provided by the R-enantiomer

(i) At a 1:3 ratio

A solid dispersion was made that had a 1:3 ratio by weight of R-4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide (100% of the R-enantiomer): HP55S enteric polymer. Production was by a spray drying method. A second solid dispersion was also made by a spray drying method, but this solid dispersion had a 1:3 ratio by weight of bicalutamide (ie, racemic 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide) : HP55S.

In vitro Dissolution Test

The test was performed following the protocol above. Figure 5 shows a comparison of cumulative % 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide released *v.* time for the two formulations and for a conventional 50mg bicalutamide tablet formulation. As Fig. 5 shows, the solid dispersion according to the invention, which had 100% of the R-enantiomer, displayed enhanced drug release compared to the conventional formulation. The enhancement was similar to that achieved by the bicalutamide solid dispersion.

(ii) At a 1:1 ratio

The protocol in part (i) was followed, with the exception that the drug : HP55S ratio for both formulations was changed to 1:1.

In vitro Dissolution Test

The test was performed following the protocol above. Figure 6 shows a comparison of cumulative % 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide released *v.* time for the two formulations with a 1:1 ratio. Again, both solid dispersion formulations displayed enhanced drug release compared to the conventional formulation. Indeed, the formulation according to the invention achieved 100% of drug in solution and supersaturation was maintained over the 60 minute test (ie, no drug precipitation was observed).

Enhancement of storage stability provided by the R-enantiomer

Solid dispersion formulations were prepared as in part B(i) above (ie, having a 1:3 ratio of drug : HP55S).

The storage stability of the formulations was assessed using X-ray diffraction (XRD) as follows. The formulations were placed in sealed glass amber vials and stored at the following conditions, 4°C, 25°C/60%RH, 50°C and 40°C/75%RH (RH, relative humidity) for three months. After three months the samples were removed and analysed by XRD (X-ray diffraction) to determine the presence or absence of crystallinity. The results are presented in the following table.

Drug:Polymer ratio	**Storage condition**	**Three months XRD**
1:3 (R/S- drug)	Initial	X
	4°C	X
	25°C/60%RH	X
	50°C	√
	40°C/75%RH	√
1:3 (R- drug)	Initial	X
	4°C	X
	25°C/60%RH	X
	50°C	X
	40°C/75%RH	X

X = no crystallinity

√ = crystallinity

As the results show, no crystallinity was detected after 3 months when the formulation according to the invention was stored under any of the conditions, indicating the superior stability of the formulation. With the bicalutamide (R/S-) formulation, however, the formulation was less stable, as indicated by the presence of crystallinity. The presence of crystallinity in the R/S sample stored at 40°C/75%RH corresponded with a reduction in the dissolution performance of the formulation when tested after 3 months of storage.

CLAIMS:

1. A pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

2. The formulation according to claim 1, wherein the enteric polymer is selected from the group consisting of: hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxpropyl methylcellulose acetate pthalate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose succinate a methacrylic acid copolymer, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), methylcellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), cellulose proprionate pthalate, hydroxypropyl cellulose butyrate pthalate, hydroxypropyl cellulose acetate pthalate succinate, hydroxypropyl methylcellulose trimellitate, cellulose acetate trimellitate (CAT), methylcellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose proprionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terepthalate and cellulose acetate isopthalate, or any combination thereof.

3. The formulation according to claim 1, wherein the enteric polymer is selected from the group consisting of: HPMCP grade HP-50, HPMCP grade HP-55, HPMCP grade HP-55S, HPMCAS grade AS-LF, HPMCAS grade AS-MF, HPMCAS grade AS-HF, HPMCAS grade AS-LG, HPMCAS grade AS-MG, HPMCAS grade AS-HG, methacrylic acid copolymer grade A and methacrylic acid copolymer grade B, or any combination thereof.

4. The formulation according to claim 1, wherein the enteric polymer is selected from the group consisting of: HPMCP grade HP-55S, HPMCAS grade AS-LG and methacrylic acid copolymer grade A.

5. The formulation according to claim 1, wherein the enteric polymer is HP-55S.

6. A pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with HP-55S enteric polymer, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

7. The formulation according to any preceding claim, wherein the weight ratio of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide : enteric polymer is from 1:0.25 to 1:10.

8. The formulation according to any preceding claim, wherein the solid dispersion comprises a wetting agent.

9. A pharmaceutical dose of 5 to 1000 mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

10. The dose according to claim 9, wherein the enteric polymer is as defined in any one of claims 2 to 5.

11. The dose according to claim 9 or 10, wherein the weight ratio of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide : enteric polymer is from 1:0.25 to 1:10.

12. The dose according to any one of claims 9 to 11, wherein the solid dispersion comprises a wetting agent.

13. The formulation or dose according to any of the preceding claims wherein ≥60%, ≥70%, ≥80%, ≥85%, ≥90%, ≥95%, ≥98% or ≥99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-

fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

14. The formulation or dose according to any of the preceding claims wherein at least 30%, 40%, 50%, 75%, 90%, 95% or 99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in amorphous form.

15. A solid dispersion of an enteric polymer having a pK_a from 3 to 6 with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

16. The solid dispersion according to claim 15, wherein the enteric polymer is as defined in any one of claims 2 to 5.

17. The solid dispersion according to claim 15 or 16, wherein the solid dispersion comprises a wetting agent.

18. The solid dispersion according to any of claims 15 to 17, wherein ≥60%, ≥70%, ≥80%, ≥85%, ≥90%, ≥95%, ≥98% or ≥99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

19. The solid dispersion of any of claims 15 to 18, wherein at least 30%, 40%, 50%, 75%, 90%, 95% or 99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in amorphous form.

20. A method for treating prostate cancer and/or reducing the risk of prostate cancer in a patient comprising administering to a patient in need thereof of a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-

fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

21. A method for treating prostate cancer and/or reducing the risk of prostate cancer in a patient comprising administering to a patient in need thereof of a pharmaceutical dose of 5 to 1000 mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein the dose comprises 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a solid dispersion comprising an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

22. A method for increasing the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in a patient comprising administration to the patient an effective amount of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in the form of the R-enantiomer.

23. A method for enhancing the storage stability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein at least 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in amorphous form, comprising use of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide wherein greater than 50% is in the form of the R-enantiomer.

24. A method for preparing a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide with reduced inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and/or increased

bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the patient comprising forming a solid dispersion of an enteric polymer having a pK_a from 3 to 6 with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

25. The method according to claim 20 or 24, wherein the formulation is provided as a daily dose of 5 to 1000 mg of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

26. The method according to any of claims 20 to 25, wherein the weight ratio of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide : enteric polymer is from 1:0.25 to 1:10.

27. The method according to any of claims 20 to 26, wherein the solid dispersion includes a wetting agent.

28. The method according to any of claims 20 to 27, wherein ≥60%, ≥70%, ≥80%, ≥85%, ≥90%, ≥95%, ≥98% or ≥99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

29. The method according to any of claims 20, 21 and 23 to 28, wherein at least 30%, 40%, 50%, 75%, 90%, 95% or 99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in amorphous form.

30. Use of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a medicament for treating prostate cancer and/or

reducing the risk of prostate cancer in the patient.

31. Use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a medicament with reduced inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide for patients in need of treatment with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

32. Use of greater than 50% of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the form of the R-enantiomer in the manufacture of a pharmaceutical formulation comprising 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in solid dispersion with an enteric polymer having a pK_a from 3 to 6.

33. Use of an enteric polymer having a pK_a from 3 to 6 in solid dispersion with 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide, wherein greater than 50% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer, in the manufacture of a pharmaceutical formulation administrable to a patient, for enhancing the storage stability of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the formulation in addition to increasing the bioavailability of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide in the patient and/or reducing inter-patient variability in plasma concentrations of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

34. The use according to any one of claims 30 to 33, wherein the medicament or pharmaceutical formulation is provided as a daily dose of 5 to 1000 mg 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

35. The use according to any one of claims 30 to 34, wherein the weight ratio of 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide : enteric polymer is from 1:0.25 to 1:10.

36. The use according to any one of claims 30 to 35, wherein the solid dispersion includes a wetting agent.

37. The use according to any one of claims 30 to 36, wherein ≥60%, ≥70%, ≥80%, ≥85%, ≥90%, ≥95%, ≥98% or ≥99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is provided in the form of the R-enantiomer.

38. The use according to any one of claims 30 to 37, wherein at least 30%, 40%, 50%, 75%, 90%, 95% or 99% of the 4′-cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide is in amorphous form.