Body weight and safety parameters did not change. During treatment with estetrol libido decreased in 8 of 20 men and nipple tenderness was reported by 7 of 20 men.

SUMMARY

The present disclosure provides an adjuvant therapy for use in prostate cancer treatment by ADT that further decreases total and free testosterone levels, achieves effective estrogen supplementation and mitigates the negative side effects of ADT.

More particularly, the disclosure relates to a treatment of prostate cancer that comprises simultaneous oral administration, alongside the ADT, of an estetrol component in a high daily dose of at least 20 mg for at least 4 weeks, said estetrol component being selected from estetrol; esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; and combinations thereof. The present disclosure revolves around a number of surprising findings by the applicant.

Firstly, co-administration of the estetrol component in a high daily oral dose of at least 20 mg during a period of at least 4 weeks results in a pronounced additional decrease of T levels, especially of biologically active free T levels.

Secondly, co-administration of the estetrol component according to the disclosure effectively mitigates hypoestrogenic symptoms which are induced in prostate cancer patients by ADT.

Thirdly, co-administration of the estetrol component as described herein decreases the risk of arterial cardiovascular disease. This is further explained below in the context of the “improved lipid profile” which is observed in prostate cancer patients that have been treated in accordance with the present disclosure.

In case the ADT employs a GnRH agonist, combining the start of GnRH agonist administration with oral administration of the estetrol component offers the advantage that LH synthesis is inhibited immediately, thereby suppressing the initial increase of LH and T levels (the flare). This flare delays castration and causes exacerbation of the symptoms.

In one aspect, the present disclosure refers to use of estetrol in the manufacture of a medicament for use in androgen deprivation therapy for the treatment of prostate cancer in a patient, wherein said medicament is to be orally administered in combination with a GnRH agonist or a GnRH antagonist to provide a daily dose of 20 mg to 80 mg for at least 4 weeks.

In another aspect, the present disclosure refers to a pharmaceutical dosage unit adapted for oral administration, comprising as a first active ingredient from 20 to 80 mg of estetrol; and as a second active ingredient a GnRH antagonist.

In another aspect, the present disclosure refers to a kit-of-parts comprising a first pharmaceutical composition comprising a GnRH agonist or a GnRH antagonist; and a second pharmaceutical composition adapted for oral administration, comprising 20 to 80 mg of estetrol.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates key sex hormone parameters measured during the clinical study described in Example 1. In particular, Figure 1A relates to Free Testosterone, Figure 1B to Total Testosterone, Figure 1C to Sex Hormone-Binding Globulin (SHBG), Figure 1D to Luteinizing Hormone (LH), and Figure 1E to Follicle Stimulating Hormone (FSH). For all

CLAIMS

1. Use of estetrol in the manufacture of a medicament for use in androgen deprivation therapy for the treatment of prostate cancer in a patient, wherein said medicament is to be orally administered in combination with a GnRH agonist or a GnRH antagonist to provide a daily dose of 20 mg to 80 mg for at least 4 weeks.

2. The use according to claim 1, wherein the medicament is to be orally administered in combination with a GnRH agonist of the androgen deprivation therapy.

3. The use according to claim 1, wherein a dosage unit comprising a GnRH antagonist of the androgen deprivation therapy is to be administered orally, together with estetrol.

4. The use according to any one of the preceding claims, wherein the estetrol is to be co-administered in a daily dose of not more than 60 mg.

5. The use according to any one of the preceding claims, wherein estetrol is to be co-administered once daily for at least 12 weeks.

6. A pharmaceutical dosage unit adapted for oral administration, comprising as a first active ingredient from 20 to 80 mg of estetrol; and as a second active ingredient a GnRH antagonist.

7. The pharmaceutical dosage unit according to claim 6, wherein the dosage unit contains not more than 60 mg estetrol.

8. A kit-of-parts comprising a first pharmaceutical composition comprising a GnRH agonist or a GnRH antagonist; and a second pharmaceutical composition adapted for oral administration, comprising 20 to 80 mg of estetrol.

9. The kit-of-parts according to claim 8, wherein the second pharmaceutical composition contains not more than 60 mg estetrol.

10. The kit-of-parts according to claim 8 or 9, wherein the first pharmaceutical composition comprises a GnRH agonist.