ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Marketing Authorisation Holders

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
AT - Austria	Astra Zeneca Österreich GmbH Schwarzenbergplatz 7 1037 Wien	Casodex	150 mg	film-coated tablet	oral use
AT - Austria	Genericon Pharma Ges.m.b.H. Hafnerstraße 211 8054 Graz	Bicalutamid "Genericon"	150 mg	film-coated tablet	oral use
AT - Austria	Genericon Pharma Ges.m.b.H. Hafnerstraße 211 8054 Graz	Bicalutanorm "Genericon"	150 mg	film-coated tablet	oral use
AT - Austria	Ratiopharm Arzneimittel Vertriebs-GmbH Albert-Schweitzer Gasse 3 1140 Wien	Bicalutamid-ratiopharm	150 mg	film-coated tablet	oral use
BE - Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel	Casodex	150 mg	film-coated tablet	oral use
BG - Bulgaria	AstraZeneca UK Ltd, 600 Capability Green Luton, Bedfordshire, LU1 3LU, UK	Casodex	150 mg	film-coated tablet	oral use
CS - Czech Republic	AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Casodex	150 mg	film-coated tablet	oral use
CS - Czech Republic	Ingers Industrial Solutions S.R.O. BRNO Jeneweinova 51a	Bicaluplex	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	617 00 Brno				
CY - Cyprus	AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Casodex	150 mg	film-coated tablet	oral use
DA - Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund	Casodex	150 mg	film-coated tablet	oral use
EL - Greece	Astrazeneca SA 4 Theotocopoulou & Astronauton 151 25 Marousi-Athens	Casodex	150 mg	film-coated tablet	oral use
EL - Greece	Dermos Meπε -pharmaceitica 25 Paraschou str. Athens	Verodex	150 mg	film-coated tablet	oral use
EL - Greece	Alvia SA 18th klm Athens-Marathon Ave 153 44 Pallini Attiki	Bicalut	150 mg	film-coated tablet	oral use
EL - Greece	Genepharm SA 18th klm Marathon Ave 153 44 Pallini Attiki	Bicamide / Genepharm	150 mg	film-coated tablet	oral use
ET - Estonia	Astrazeneca UK Ltd. Stanhope Gate 15 London W1K 1LN United Kingdom	Casodex	150mg	film-coated tablet	oral use
FI - Finland	AstraZeneca Oy Luomanportti 3 02200 Espoo	Casodex	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
FI - Finland	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Lukasenomid	150 mg	film-coated tablet	oral use
FI - Finland	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Bicalutamid CT-Arzneimittel	150 mg	film-coated tablet	oral use
FI - Finland	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Bicalutamid Ratiopharm	150 mg	film-coated tablet	oral use
FI - Finland	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Bicalutamid Ribosepharm	150 mg	film-coated tablet	oral use
FI - Finland	Avansor Pharma Oy Tekniikantie 14 02150 Espoo	Bicavan	150 mg	film-coated tablet	oral use
FI - Finland	Synthon B V Microweg 22 6545 GN Nijmegen The Netherlands	Bikalutamidi Synthon	150 mg	film-coated tablet	oral use
FI - Finland	Alternova Oy Ab Rajatorpantie 41 C 01640 Vantaa	Bicalutamid Alternova	150 mg	film-coated tablet	oral use
FI - Finland	Peseri Trading Limited El Greco House	Alidex	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	20 Queen Frederiks Street, Office 301 1066 Nicosia, Cyprus				
FI - Finland	Peseri Trading Limited El Greco House 20 Queen Frederiks Street, Office 301 1066 Nicosia, Cyprus	Bicadex	150 mg	film-coated tablet	oral use
FI - Finland	Orion Corporation Orionintie 1, PO Box 65 02101 Espoo	Bicalutamid Orion	150 mg	film-coated tablet	oral use
FI - Finland	Peseri Trading Limited El Greco House 20 Queen Frederiks Street, Office 301 1066 Nicosia, Cyprus	Bicalutamide Peseri	150 mg	film-coated tablet	oral use
FI - Finland	Tad Pharma GmbH Heinz-Lohmann-Strasse 5 27472 Cuxhaven, Germany	Bicatad	150 mg	film-coated tablet	oral use
FI - Finland	Peseri Trading Limited El Greco House 20 Queen Frederiks Street, Office 301 1066 Nicosia, Cyprus	Biclad	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Duralutamide	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Grelutamide	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28	Henlutamide	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	20097 Hamburg, Germany				
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Inatamide	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Konlutamide	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Saputamide	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Skylutamide	150 mg	film-coated tablet	oral use
FI - Finland	Helm Pharmaceuticals GmbH Nordkanalstr. 28 20097 Hamburg, Germany	Timutamide	150 mg	film-coated tablet	oral use
FI - Finland	Peseri Trading Limited El Greco House 20 Queen Frederiks Street, Office 301 1066 Nicosia, Cyprus	Lutamide	150 mg	film-coated tablet	oral use
FR - France	AstraZeneca 1, place Renault 92844 Rueil-Malmaison Cedex	Casodex	150 mg	film-coated tablet	oral use
HU - Hungary	Pharmaconsult Kft.: 1141 Budapest, Ráskay Lea u. 44. Hungary	Bilutamid	150 mg	film-coated tablet	oral use
HU - Hungary	AstraZeneca KFt. Park u. 3 Törökbálint	Casodex	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	H-2045				
IS - Iceland	AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Casodex	150mg	film-coated tablet	oral use
IT - Italy	Astrazeneca S.P.A. Palazzo Volta Via F. Sforza 20080 - Basiglio (MI)	Casodex	150 mg	film-coated tablet	oral use
LT - Lithuania	AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Casodex	150 mg	film-coated tablet	oral use
LU - Luxembourg	NV AstraZeneca SA 110 rue E. Van Ophem B-1180 Bruxelles Belgium	Casodex	150 mg	film-coated tablet	oral use
LV - Latvia	AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Casodex	150 mg	film-coated tablet	oral use
NO - Norway	AstraZeneca AS Boks 200 Vinderen 0319 Oslo	Casodex	150mg	film-coated tablet	oral use
PL - Poland	AstraZeneca UK Limited	Casodex	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom				
PT - Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, 7 Valejas - 2745-663 Barcarena	Casodex	150 mg	film-coated tablet	oral use
PT - Portugal	Generis Farmacêutica, S.A. Office Park da Beloura - Edifício 4 Quinta da Beloura 2710-444 Sintra	Bicalutamida Generis	150 mg	film-coated tablet	oral use
PT - Portugal	Generis Farmacêutica, S.A. Office Park da Beloura - Edifício 4 Quinta da Beloura 2710-444 Sintra	Bicalutamida Prostec	150 mg	film-coated tablet	oral use
PT - Portugal	Farma-APS, Produtos Farmacêuticos, S.A. Rua João de Deus, 19 Venda Nova 2700-487 Amadora	Bicalutamida Etsi	150 mg	film-coated tablet	oral use
RO-Romania	AstraZeneca UK Ltd, 600 Capability Green Luton, Bedfordshire, LU1 3LU, UK	Casodex	150 mg	film-coated tablet	oral use
SK – Slovakia	AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Casodex	150 mg	film-coated tablet	oral use
SL - Slovenia	AstraZeneca UK Limited	Casodex	150 mg	film-coated tablet	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
SV - Sweden	15 Stanhope Gate London, W1K 1LN United Kingdom AstraZeneca AB Västra Mälarehamnen 9 SE-151 85 Södertälje	Casodex	150 mg	film-coated tablet	oral use
UK - United Kingdom	AstraZeneca UK Limited Horizon Place 600 Capability Green Luton, Bedfordshire LU1 3LU	Casodex	150 mg	film-coated tablet	oral use
UK - United Kingdom	AstraZeneca UK Limited Horizon Place 600 Capability Green Luton, Bedfordshire LU1 3LU	Bicalutamide	150 mg	film-coated tablet	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BICALUTAMIDE 150 mg CONTAINING MEDICINAL PRODUCTS (see Annex I)

Background

Bicalutamide is an oral anti-androgen used in the management of prostate cancer. Bicalutamide 150 mg is marketed in the EU following national and Mutual Recognition application procedures. Its authorised indications include the treatment of patients with locally advanced prostate cancer, as an immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy. Locally advanced prostate cancer refers to larger tumours or tumours with spread to lymph nodes, but not involving spread to other organs.

In 2004, 2 publications were published detailing a pre-planned 2nd analysis of the Casodex (bicalutamide) Early Prostate Cancer (EPC) study programme.

These same data were considered by the UK, the Reference Member State (RMS) for the Mutual Recognition Procedure (MRP), in 2003. At that time, the RMS concluded that Casodex (bicalutamide) 150 mg should not be used in the treatment of 'localised' prostate cancer, however, it was concluded that the benefit/risk balance remained positive for selected patients in 'locally advanced' prostate cancer, as immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy. Section 5.1 of the SPC was amended to note that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, might be to defer hormonal therapy until signs that the disease is progressing.

Following their own review of these data carried out in 2004 and due to their resulting concerns over the benefit/risk balance of bicalutamide 150 mg in locally advanced prostate cancer, the Belgian Regulatory Authority suspended their national Marketing Authorisation for Casodex (bicalutamide) 150 mg in August 2005.

In view of the concerns related to safety and efficacy for bicalutamide 150 mg the National Competent Authority (NCA) in Belgium considered it to be in the interest of public health to perform a new benefit/risk assessment. Therefore, Belgium referred the issue on 27 July 2006 for consideration by CHMP under Article 31 of Directive 2001/83/EC, as amended.

The 4 issues raised in the referral concern the analyses of the Early Prostate Cancer Programme (EPC):
- the lack of an overall survival benefit versus adverse events in 'locally advanced prostate cancer';
- statistical concerns regarding multiplicity;
- the standard of care for the placebo group in the relevant studies;
- the number of deaths due to cardiac failure.

Based on the concerns raised, the following questions were posed to the Applicants/ MAHs as part of the consolidated CHMP List of Questions, the responses to which were the basis of the CHMP reassessment of the benefit/risk balance:

1/ How does the company justify the indication of bicalutamide 150 mg for locally advanced prostate cancer knowing the absence of statistically significant overall survival and the important side effects?
2/ How does the company justify the absence of adjustment for tests of multiplicity in the analysis of the EPC results?
3/ How does the company justify that the placebo arm did not receive an adequate treatment according to the present standard of care and why this is not taken into account in the analysis of the EPC results?
4/ How can the company rule out any role of bicalutamide 150 mg in the increased mortality due to heart failure in the Casodex arm of the EPC trial?

The scope of the referral included all pending Marketing Authorisation applications as well as all Marketing Authorisations for medicinal products containing 150 mg bicalutamide. Further, the referral concerned only

the locally advanced prostate cancer indication based on the Early Prostate Cancer study programme, and the directly related wording in sections 4.1 and 5.1 of the SPC.
Other aspects of the SPC and the other indication for bicalutamide 150 mg, which is approved in some EU member states, were not within the scope of the referral.

Benefit/ Risk considerations

When the EPC programme was initiated more than 8 years ago, the aim was to document the benefit of early bicalutamide therapy versus placebo as monotherapy or adjuvant therapy to surgery or radiotherapy. The lack of broad consensus in the standard of care for early prostate cancer makes it difficult to study. The EPC study was an empirical design, that is to say, it generally compared Casodex (bicalutamide) to the standard of care in each region involved.

It is acknowledged that overall there is no statistically significant survival benefit in locally advanced prostate cancer. However, the EPC study was positive for the primary progression free survival (PFS) endpoint, both overall and in the locally advanced subgroups.

At the initial authorisation of the early prostate cancer indication, the data for overall survival were too immature to allow an analysis, however it makes sense to subsequently analyse this endpoint in the same subgroups, and there are favourable trends in overall survival for patients with locally advanced disease receiving Casodex (bicalutamide) alone, and for patients also receiving radiotherapy.

As regards the multiplicity issue raised, it is considered appropriate to look at subgroups from a statistical viewpoint, as they have helped to narrow the indication to patients with a more favourable benefit/risk balance for bicalutamide 150 mg. These are also not arbitrary subgroups, but are implicit in the proposed indication, correspond to the way prostate cancer is classified, managed and studied, and the results are consistent with what might be expected. It seems intuitive that for good prognosis patients who have also received treatment of curative intent, the addition of bicalutamide might confer less benefit than in other patients. In addition, the survival advantage observed in patients with locally advanced disease receiving radiotherapy appears to be consistent with that seen in previous studies, and a synergistic effect with radiotherapy is plausible. It is difficult to obtain overall survival data in patients with early prostate cancer due to its insidious course. For these reasons, the CHMP considers that the progression-free survival results are important and can be considered on their merits. Disease progression may be associated with problems such as painful bone metastases, cord compression, pathological fractures and urinary obstruction. The PFS results are given again below:

Progression-free survival in locally advanced disease by therapy sub-group

Analysis population	***Events (%) in Casodex patients***	***Events (%) in placebo patients***	***Hazard ratio (95% CI)***
Watchful waiting	*193/335 (57.6)*	*222/322 (68.9)*	*0.60 (0.49 to 0.73)*
Radiotherapy	*66/161 (41.0)*	*86/144 (59.7)*	*0.56 (0.40 to 0.78)*
Radical prostatectomy	*179/870 (20.6)*	*213/849 (25.1)*	*0.75 (0.61 to 0.91)*

In particular, there is a statistically significant and clinically meaningful improvement in progression-free survival in the patients with locally advanced prostate cancer who received Casodex (bicalutamide) as compared to placebo (58% versus 69% progressors in patients who were not receiving adjuvant surgery or radiotherapy).

Benefit is generally a function of risk progression and in patients with locally advanced disease; benefit is reduced after surgery or in cases where radiotherapy is likely to be curative.

With reference to the adequacy of treatment in the placebo group in the EPC studies, given that at the time of initiation of these studies there was no widely agreed standard of care in locally advanced prostate cancer (something which remains the case), the empirical design of the studies, which compared Casodex (bicalutamide) 150mg or placebo when given as an adjunct to “standard care” is considered reasonable.

None of the EPC trials mandated that treatment be withheld from patients in the placebo group until clinical progression. The median PSA levels on initiation of active therapy for each subgroup are above the thresholds in current European Association of Urology (EAU) guidance.

These results should of course be balanced against the well-known tolerability issues of Casodex (bicalutamide). Gynaecomastia and breast pain have been highlighted (mainly in the 1st year of intake) and can be managed in many patients. In the clinical studies this was severe in around 5% of patients. Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment. EAU guidelines suggest the use of prophylactic breast radiation, tamoxifen or aromatase inhibitors to manage these symptoms, although they are not licensed in this use.

The requested additional analyses of the EPC trial data confirm an increased risk for deaths coded as heart failures (however, with no overall excess risk in the cardiovascular system), an increased risk of urogenital symptoms (including gynaecomastia and breast pain) mainly during the first year of intake, and further indicate the absence of an adverse effect on thromboembolic events during the follow-up (supported by a pattern of events inconsistent with hormonal effects). There was no evidence of an overall excess mortality.

With reference to heart failure mortality, the MAHs have submitted a limited amount of new data since this issue was last assessed, namely results from a further clinical study, an updated literature review and an updated review of their safety database. The numbers involved are relatively small, there is no consistent pattern for heart failure deaths over the longer term, and there is some unreliability in selecting this as a cause of death. However, an association with bicalutamide cannot be ruled out.
Whilst the pattern of adverse events argues against a role for raised oestrogen levels, it is known that the myocardium has androgen receptors, and it might be affected by long-term androgen deprivation. However, the numbers of cases involved are relatively small, and there is no clear temporal relationship.
The majority of patients with heart failure had confounding factors at study entry, and the causality assessment of investigators for all deaths ascribed to heart failure was "not related". Regarding the heart failure deaths, the allocation of cause of death is known to be unreliable, and very few post-mortems were done.

Due to a small number of relevant subjects, no conclusions could be drawn regarding the contribution of tamoxifen or radiotherapy to cardiovascular outcomes, or on whether tamoxifen exposure had a synergistic effect on efficacy. However, it is not possible to entirely "rule out" thromboembolic events as contributory explanation of increased cardiovascular mortality.

The need to further study cardiovascular morbidity and mortality remains. A new pharmacoepidemiological study will be undertaken as part of an agreed Risk Management Plan (RMP), a post-opinion commitment to get a better understanding of cardiovascular risk. The aim of the study is to estimate the incidence of heart failure, cardiovascular morbidity and mortality in patients with prostate cancer, compared to the general population. Further, the study will include prostate cancer subgroups to include those on Casodex (bicalutamide), and those treated with luteinizing hormone-releasing hormone (LHRH) analogues, orchidectomy, and other hormonal therapies.
The 4th analysis of the EPC data will also be provided when available.

In conclusion, the heart failure data remain a concern and are inconclusive, but do not significantly alter the benefit/risk balance in locally advanced prostate cancer patients. However, these data do support the Committee's position that the indication should be restricted to selected patients with locally advanced prostate cancer at high risk of disease progression.

How such patients are identified could be based on criteria such as PSA levels, Gleason score and stage of disease. A more specific target population is hard to define from the EPC data, and the general term "high risk" better accommodates wide differences in local practice and inevitable changes in the standard of care, and takes into account the many variables in the individual patient which may contribute to risk of progression. Patients and clinicians should decide on the most appropriate treatment on an individual basis, discussing efficacy and tolerability aspects of all available treatments, all available risk factors for disease progression, and taking into account the lifestyle of the patient. The SPC has been amended accordingly and notes in section 5.1 that, for patients with locally advanced disease "A reduction in risk of objective disease progression… was most evident in those at highest risk of disease progression. Therefore, clinicians may

decide that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, may be to defer hormonal therapy until signs that the disease is progressing." Section 5.1 of the SPC also includes a summary of the efficacy results from the EPC study.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing bicalutamide 150 mg.

- The Committee considered that bicalutamide 150 mg is effective in the treatment of locally advanced prostate cancer; however the CHMP considered that the therapeutic indication should be restricted to treatment of patients at high risk of disease progression.

- In view of the available data, the CHMP concluded that a potential association between the use of bicalutamide 150 mg and heart failure cannot be ruled out and therefore considered that the need to further study cardiovascular morbidity and mortality remains. To address this concern, a new epidemiological study will be performed, as part of an agreed Risk Management Plan.

- The CHMP concluded that the benefit/risk balance of bicalutamide 150 mg containing medicinal products in the agreed restricted indication is favourable.

As a consequence, the CHMP has recommended to maintain the Marketing Authorisations for all medicinal products and to grant Marketing Authorisations for all applications referred to in Annex I of the Opinion in accordance with the amendments to the relevant sections of the Summary of Product Characteristics, set out in Annex III of the Opinion.

ANNEX III

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS

Note: This Annex III (Amendments to the Summary of Product Characteristics) is the one that was Annexed to the Commission Decision on this Article 31 referral for bicalutamide 150 mg containing medicinal products.
The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update Annex III as required. Therefore, Annex III may not necessarily represent the current text.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTION OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR BICALUTAMIDE 150MG CONTAINING MEDICINAL PRODUCTS

[…..]

4.1 Therapeutic indications

[Invented name] 150mg is indicated either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression (see section 5.1).

[…..]

5.1 Pharmacodynamic properties

[…..]

CASODEX (Bicalutamide) 150 mg was studied as a treatment for patients with localised (T1-T2, N0 or NX, M0) or locally advanced (T3-T4, any N, M0; T1-T2, N+, M0) non-metastatic prostate cancer in a combined analysis of 3 placebo controlled double-blind studies in 8113 patients, where CASODEX was given as immediate hormonal therapy or as adjuvant to radical prostatectomy or radiotherapy, (primarily external beam radiation). At 7.4 years median follow up, 27.4% and 30.7% of all CASODEX and placebo-treated patients, respectively, had experienced objective disease progression.

A reduction in risk of objective disease progression was seen across most patient groups but was most evident in those at highest risk of disease progression. Therefore, clinicians may decide that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, may be to defer hormonal therapy until signs that the disease is progressing.

No overall survival difference was seen at 7.4 years median follow up with 22.9% mortality (HR=0.99; 95% CI 0.91 to1.09). However, some trends were apparent in exploratory subgroup analyses.

Progression-free survival and overall survival data for patients with locally advanced disease are summarised in the following tables:

Table 1 Progression-free survival in locally advanced disease by therapy sub-group

Analysis population	Events (%) in CASODEX patients	Events (%) in placebo patients	Hazard ratio (95% CI)
Watchful waiting	193/335 (57.6)	222/322 (68.9)	0.60 (0.49 to 0.73)
Radiotherapy	66/161 (41.0)	86/144 (59.7)	0.56 (0.40 to 0.78)
Radical prostatectomy	179/870 (20.6)	213/849 (25.1)	0.75 (0.61 to 0.91)

Table 2 Overall survival in locally advanced disease by therapy sub-group

Analysis population	Deaths (%) in CASODEX patients	Deaths (%) in placebo patients	Hazard ratio (95% CI)
Watchful waiting	164/335 (49.0)	183/322 (56.8)	0.81 (0.66 to 1.01)
Radiotherapy	49/161 (30.4)	61/144 (42.4)	0.65 (0.44 to 0.95)
Radical prostatectomy	137/870 (15.7)	122/849 (14.4)	1.09 (0.85 to 1.39)

For patients with localised disease receiving CASODEX alone, there was no significant difference in progression free survival. In these patients there was also a trend toward decreased survival compared with

placebo patients (HR=1.16; 95% CI 0.99 to 1.37). In view of this, the benefit-risk profile for the use of CASODEX is not considered favourable in this group of patients.

[…..]

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

National Competent Authorities (NCA), coordinated by the Reference Member State (RMS), shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

- A new pharmacoepidemiological study(ies) should be undertaken to get a better understanding of cardiovascular risk. The aim of the study should be to estimate the incidence of heart failure, cardiovascular morbidity and mortality in patients with prostate cancer, compared to the general population. Further, the study should include prostate cancer subgroups to include those on bicalutamide, and those treated with LHRH analogues, orchidectomy, and other hormonal therapies. The results should be reported to the RMS and the NCAs where bicalutamide 150 mg is authorised.

- The outcome of the 4th analysis of the EPC data should be provided to the RMS and the NCAs where bicalutamide 150 mg is authorised.

- For all MAHs, in addition to routine pharmacovigilance activities, identified and potential risks highlighted for increased monitoring and follow-up should include:

  Heart failure
  Hepatic failure
  Interstitial lung disease
  Breast cancer
  Reports concerning pregnancy in partners of patients taking bicalutamide