ANNEX I

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

Member State	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical form	Route of administration
Austria		TEVA Pharma B.V., Industrieweg 23, P.O. Box 217 3640 AE Mijdrecht The Netherlands	Bicalutamid-TEVA 150 mg-Filmtabletten	150 mg	Film-coated tablet	Oral use
Czech Republic	Ingers Industrial Solutions s. r.o. Jeneweinova 51a, 617 00 Brno, Czech Republic		Bicaluplex 150 mg	150 mg	Film-coated tablet	Oral use
Germany		Ingers Industrial Solutions s. r.o. Jeneweinova 51a, 617 00 Brno, Czech Republic	Bicamid-GRY 150 mg Filmtabletten	150 mg	Film-coated tablet	Oral use
Denmark		TEVA Sweden AB PO Box 1070, SE - 25110 Helsingborg Sweden	Bicalutamid TEVA	150 mg	Film-coated tablet	Oral use
Estonia		TEVA Pharma B.V., Industrieweg 23, P.O. Box 217 3640 AE Mijdrecht The Netherlands	Bicalutamide-TEVA	150 mg	Film-coated tablet	Oral use

Greece		TEVA Pharma B.V., Industrieweg 23, P.O. Box 217 3640 AE Mijdrecht The Netherlands	Bicalutamide Teva 150 mg Επικαλυμμένα με λεπτό υμένιο δισκία	150 mg	Film-coated tablet	Oral use
France		TEVA Classics S.A. 1, cours du Triangle, Immeuble Palatin 1, 92936 Paris La Défense cedex 12 France	Bicalutamide Teva 150 mg, comprimés pelliculés	150 mg	Film-coated tablet	Oral use
Hungary		TEVA Magyarország Rt Rákóczi út 70-72, Budapest, H-1074, Hungary	Bicalutamid-Teva	150 mg	Film-coated tablet	Oral use
Italy		TEVA Pharma Italia S.R.L. Viale G. Richard 7, 20143 Milano Italy	Bicalutamide TEVA 150 mg compresse rivestite con film	150 mg	Film-coated tablet	Oral use
Latvia		TEVA Pharma B.V., Industrieweg 23, P.O. Box 217 3640 AE Mijdrecht The Netherlands	Bicalutamide-TEVA	150 mg	Film-coated tablet	Oral use
Lithuania		TEVA Pharma B.V., Industrieweg 23, P.O. Box 217 3640 AE Mijdrecht The Netherlands	Bicalutamide -Teva 150 mg plėvele dengtos tabletės	150 mg	Film-coated tablet	oral use

The Netherlands		Pharmachemie B.V. Swensweg 5, Postbus 552, 2003 RN Haarlem The Netherlands	Bicalutamide 150 PCH, filmomhulde tabletten 150 mg	150 mg	Film-coated tablet	Oral use
Norway		TEVA Sweden AB PO Box 1070, SE - 25110 Helsingborg Sweden	Bicalutamid TEVA 150 mg tabletter, filmdrasjerte	150 mg	Film-coated tablet	Oral use
Poland	Ingers Industrial Solutions s. r.o. Jeneweinova 51a, 617 00 Brno, Czech Republic		Bicalutamide Ingers 150 mg tabletki powlekane	150 mg	Film-coated tablet	Oral use
Portugal		TEVA Pharma - Produtos Farmacêuticos Lda Lagoas Park, Edifício 1, Piso 3, 2740-264 Porto Salvo, Portugal	Bicalutamida Teva	150 mg	Film-coated tablet	Oral use
Slovakia		Ingers Industrial Solutions s. r.o. Jeneweinova 51a, 617 00 Brno, Czech Republic	Bicalutamid-Teva 150 mg	150mg	Film-coated tablet	Oral use

Slovenia		TEVA Pharma B.V., Industrieweg 23, P.O. Box 217 3640 AE Mijdrecht The Netherlands	Bikalutamid TEVA 150 mg filmsko obložene tablete	150 mg	Film-coated tablet	Oral use
Sweden		Ingers Industrial Solutions s.r.o., Jeneweinova 51 a 617 00 Brno, Tjeckien	Bicalutamide Teva 150 mg filmdragerade tabletter	150 mg	Film-coated tablet	Oral use
The United Kingdom		Ingers Industrial Solutions s.r.o., Jeneweinova 51 a 617 00 Brno, Tjeckien	Bicalutamide 150 mg Film-coated Tablets	150mg	Film-coated tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BICALUTAMIDE 150 mg CONTAINING MEDICINAL PRODUCTS

Bicalutamide 150mg film-coated tablets (Ingers Industrial Solutions s.r.o.) are generic preparations containing bicalutamide as the active substance. Bicalutamide is an oral-androgen used in the management of locally advanced prostate cancer, as an immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy.

The applicant has applied for a Marketing Authorisation in several member states through the Mutual Recognition Procedure with Czech Republic as reference member state (RMS). The Article 29 referral procedure was initiated due to concerns raised by Germany on the potential serious risk to public health regarding the benefit/risk ratio of this product. The bioequivalence between the reference and test products was sufficiently proven and was not questioned in this referral.

The scope of Bicaluplex Article 29 Referral concerns the benefit/risk ration of both indications: treatment of locally advanced prostatic cancer and monotherapy in early treatment or as adjunct to treatment with radiotherapy or radical prostatectomy in patients with prostate cancer.
The Committee, considering the Casodex Referral (bicalutamide 150 mg) made under article 31 of Directive 2001/83/EC for medicinal products containing bicalutamide, reached the conclusion that bicalutamide 150mg is effective in the treatment of locally advanced prostate cancer; however the CHMP considered that the therapeutic indication should be restricted to: “Bicalutamide 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”. The CHMP also concluded that a potential association between the use of bicalutamide 150 mg and heart failure could not be ruled out and therefore considered that the need to further study cardiovascular morbidity and mortality remains. The CHMP concluded that the benefit/risk balance of bicalutamide 150 mg containing medicinal products in the agreed restricted indication is favourable.

Based on these conclusions, the CHMP considered generic Bicalutamide 150mg film-coated tablets (Ingers Industrial Solutions s.r.o.) acceptable for registration based on a positive benefit/risk ratio of bicalutamide 150mg containing products as recently assessed in the Casodex Article 31 Referral.

Therefore, 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 and Package Leaflet, set out in Annex III of the Opinion.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

The valid summary of product characteristics is the final version achieved during the Coordination group procedure with the following amendments:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bicaluplex 150 mg tablets are 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

Pharmacotherapeutic group: anti-androgens, ATC code: L02BB03
Bicalutamide is a non-steroidal anti-androgen without any other endocrine activity. It binds to androgen receptors without activating gene expression and thus inhibits androgen stimulation. Inhibition results in the regression of prostatic tumours. Treatment discontinuation may result in anti-androgen withdrawal syndrome in some patients.

Bicalutamide is a racemate, the (R)-enantiomer of which has most of the anti-androgen activity.

Bicalutamide 150 mg was studied as a treatment for patients with localized (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 8,113 patients, where the product was given as immediate hormone therapy or as adjuvant to radical prostatectomy or radiotherapy (primarily external beam radiation). At 7.4 years median follow-up, 27.4 % of all bicalutamide-treated patients and 30.7 % of all placebo-treated patients 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% confidence interval 0.91 to 1.09). However some trends were apparent for patients 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 Bicalutamide 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 Bicalutamide 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 bicalutamide 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 bicalutamide is not considered favourable in this group of patients.

The effectiveness of bicalutamide 150 mg in the treatment of patients with locally advanced prostatic carcinoma without metastases, for whom primary treatment with hormones was indicated, was evaluated separately using the meta-analysis of two studies comprising 480 patients with prostatic carcinoma without metastases (M0) who had not been treated before. There was no significant difference in survival (HR=1.05 (CI=0.81-1.36), p=0.669) or in the interval until progression (HR=1.20 (CI 0.96-1.51), p=0.107) between the group treated with bicalutamide 150 mg and the group treated with castration. A general trend with respect to quality of life in favour of bicalutamide 150 mg in comparison with castration was observed; the subgroups that provided these data showed significantly higher sexual appetence (p=0.029) and fitness (p=0.046).

Combined analysis of 2 clinical studies comprising 805 patients with metastatic prostatic carcinoma, who had not been treated before with expected mortality 43%, showed that the treatment with bicalutamide 150 mg is less effective than castration as for the survival time (HR = 1.30 [confidence interval 1.04 – 1.65]). The estimated difference is 42 days while the mean survival time is 2 years.

LABELLING

The valid labelling text is the final version achieved during the Coordination group procedure.

PACKAGE LEAFLET

The valid package leaflet is the final version achieved during the Coordination group procedure with the following amendments:

1. WHAT BICALUTAMIDE IS AND WHAT IT IS USED FOR

Bicalutamide belongs to the group of anti-androgens. Anti-androgens act against the effects of androgens (male sex hormones).

Bicalutamide is used in adult men for the treatment of prostate cancer without metastases, when castration or other types of treatment are not indicated or unacceptable.

It may be used in combination with radiotherapy or prostate surgery in early treatment programmes.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS OF THE MARKETING AUTHORISATION

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

- 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, and reports concerning pregnancy in partners of patients taking bicalutamide.