ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT AND MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Applicant**	**Invented name**	**Strength**	**Pharmaceutical form**	**Route of administration**	**Content (concentration)**
Denmark	Valera Pharmaceuticals Ireland Ltd. 25-28 North Wall Quay, Dublin, Ireland		Vantas	50 mg	Implant	Subcutaneous	50 mg
Germany		Valera Pharmaceuticals Ireland Ltd. 25-28 North Wall Quay, Dublin, Ireland	Vantas	50 mg	Implant	Subcutaneous	50 mg
Ireland		Valera Pharmaceuticals Ireland Ltd. 25-28 North Wall Quay, Dublin, Ireland	Vantas	50 mg	Implant	Subcutaneous	50 mg
Italy		Valera Pharmaceuticals Ireland Ltd. 25-28 North Wall Quay, Dublin, Ireland	Vantas	50 mg	Implant	Subcutaneous	50 mg
Spain		Valera Pharmaceuticals Ireland Ltd. 25-28 North Wall Quay, Dublin, Ireland	Vantas	50 mg	Implant	Subcutaneous	50 mg
United Kingdom		Valera Pharmaceuticals Ireland Ltd. 25-28 North Wall Quay, Dublin, Ireland	Vantas	50 mg	Implant	Subcutaneous	50 mg

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF VANTAS (see Annex I)

Early in its natural cycle, prostate cancer is androgen dependent. Late in the clinical course, it is androgen independent, and is refractory to hormonal therapy. However, even in the androgen-independent state, prostate cancer is likely to contain subpopulations of cells that are androgen dependent. On the basis of these limited data, continued androgen suppression in men with androgen-independent prostate cancer (AIPC) is the current standard of care. In the past, testosterone suppression was achieved by bilateral orchiectomy (surgical castration). For the last two decades, injection of long-acting luteinizing hormone-releasing hormone agonists (LH-RHas) has been used to achieve androgen ablation. In principle, it is important to achieve serum testosterone concentrations as low as possible for ADT to minimize stimulation of prostate cancer cells. Serum testosterone concentrations that correspond to castration levels have generally been set at less than 50 ng/dL (1.7 nmol/L), given the known variability of values in reference laboratories. The achievement of castrate levels of testosterone is an acceptable surrogate endpoint in hormone sensitive advanced prostate cancer which can be translated into less pain from bone metastases, improvement in urinary flow, and in some cases slowing of tumour progression, although a clear-cut survival benefit has not been demonstrated. Androgen ablation is considered to be a palliative treatment. Furthermore, reduction of testosterone to castrate levels has been accepted as a valid surrogate for clinical efficacy in advanced prostate cancer by the CHMP in 2004 as part of scientific advice from the SAWP. Thus, the documented pharmacological endpoint serum testosterone < 50 ng/dL, documented for Vantas in studies 302, 301 and in addition in the Long Term Extension of Study 301 is an acceptable primary efficacy endpoint in patients with advanced prostate cancer.

With an efficacy of 98-100% in serum testosterone reduction further active comparator studies are redundant and thus not necessary. Another LHRH agonist could be used, but this is superfluous considering the meta-analysis presented by Applicant, orchidectomy is not acceptable when reversible methods are available, DES is obsolete and non-steroidal anti-androgens may have inferior efficacy when used as monotherapy.

The safety database seems limited, but no unexpected safety issues have occurred nor in the American post marketing surveillance neither in the trials. The data of the Long Term Extension of Study 301 support long-term safety for patients treated with Vantas for two or more years. A distinction should be made between safety aspects of androgen suppression therapy in general and the (local) safety of this product. The safety of androgen suppression is well known and further information is not necessary for this product. The local safety of Vantas is sufficiently investigated and further comparative studies are not necessary. The proposal of the applicant/MAH to include five pharmacovigilance safety concerns in the Risk Management Plan is endorsed (two relate specifically to the unique Vantas formulation while the other three are classified as class effects: expulsions, cellulitis, flare, osteoporosis and QT prolongation).

In conclusion, the CHMP agrees that the responses submitted by the Applicant indicate that the issues are resolved. Vantas is a new LHRH agonist and this pharmacological class was introduced for the treatment of advanced prostate cancer more than 20 years ago. There is no indication that any of the members within this class differs with respect to efficacy and safety, and Vantas seems to be no exception in that respect. The data from the *Long Term Extension Study 301* concerning efficacy and safety are in support for both long-term efficacy and safety for patients, receiving palliative treatment of advanced prostate cancer with histrelin implant for two or more years. The CHMP requests the inclusion, as proposed by the Applicant/MAH, of the five pharmacovigilance safety concerns in the Risk Management Plan as mentioned above.

The CHMP has recommended the granting of the Marketing Authorisation for which the Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure as mentioned in Annex III for Vantas.

ANNEX III

SUMMARY OF PRODUCT CHARACHTERITICS,
LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.