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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Prostap 6 DCS 30 mg Powder & Solvent for Prolonged-Release Suspension for Injection in Pre-filled Syringe
Leuprorelin Acetate
PA2229/009/002

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Prostap 6 DCS 30 mg powder and solvent for suspension for injection in pre-filled syringe, from Takeda UK limited on 8th of April 2011 for : metastatic prostate cancer; locally advanced prostate cancer, as an alternative to surgical castration; as an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer; as an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

This application is for a dual chamber pre-filled syringe. It is a line extension of PA1547/3/2, Prostap 3 3.75 mg powder and solvent for suspension for injection, presented as separate powder and solvent vials. It is submitted in line with EC regulations 1084/2003 and in line with article 8(3) of 2001/ 83EC as amended.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product	Prostap 6 DCS 30 mg powder and solvent for suspension for injection in pre-filled syringe
Name(s) of the active substance(s) (INN)	Leuprorelin Acetate
Pharmacotherapeutic classification (ATC code)	L02AE02
Pharmaceutical form and strength(s)	30 Milligram
Marketing Authorisation Number(s) in Ireland (PA)	PA2229/009/002
Marketing Authorisation Holder	Takeda Products Ireland Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Prostap 6 DCS 30 mg powder and solvent for suspension for injection in pre-filled syringe

II.2 Drug substance

The active substance is leuprorelin acetate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The product is consists of a sustained release formulation of leuprorelin acetate in a dual chamber syringe. One chamber has lyophilised powder containing the active substance and the other chamber contains the sterile solvent used to form the suspension.

Each syringe contains 30mg leuprorelin acetate. The excipients are polylactic acid, mannitol, carmellose sodium, polysorbate 80, acetic acid and water for injections.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for a sterile product that is a suspension and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as a dual chamber pre-filled syringe. It is presented with a 23 gauge syringe needle, syringe plunger and an injection site swab.

Evidence has been provided that the components of the syringe comply with Ph. Eur requirements for glass containers for sterile products and rubber stoppers.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years unopened and stored not above 25°C. The product should not be refrigerated or frozen.

Once reconstituted with the solvent the suspension should be used immediately.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of PROSTAP 6 DCS 30 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe.

III NON-CLINICAL ASPECTS

III.1 Introduction

N/A

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

N/A

IV CLINICAL ASPECTS

IV.1 Introduction

Prostate cancer is the second most common malignancy in men, accounting for approximately 10% of all male cancer deaths and its incidence is increasing.
Ablation of testosterone secretion by hormonal therapy or orchidectomy are well recognised key therapeutic interventions in prostatic carcinoma. Luteinising hormone releasing hormone (LHRH) analogues are a proven and well accepted method for achieving chemical castration. The therapeutic principle of LHRH analogues are based on its primary action on the anterior pituitary. The initial response to the first injection results in a transient stimulatory effect on testosterone secretion, but continued exposure to LHRH analogues results in a paradoxical suppression of gonadotropin release and, as a consequence, a reduction in plasma testosterone concentration to castrate levels.

Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring porcine LHRH and was first synthesized in 1974 by Takeda Chemical Industries, Japan. The peptide has a longer half-life due to its increased resistance to peptidase degradation and is about 50 – 80 times more potent than the natural LHRH due to its enhanced binding affinity to the LHRH-receptor.

The following presentations of Leuprorelin acetate are approved as national authorisations in the UK and Ireland:

- Prostap® SR first authorised in Ireland in March 1994
- Prostap®3 first authorised in Ireland in July 1998

The one-month sustained-release leuprorelin acetate preparation (Prostap® SR) has been approved for marketing in 85 countries worldwide for the treatment of sex hormone-dependent diseases such as prostate cancer, endometriosis, uterine myoma, breast cancer, and central precocious puberty. The three-month (Prostap®3) sustained-release preparation has been granted marketing approval in 58 countries worldwide. The 30 mg 6-month presentation that is the subject of this current application has been authorised via national procedures in Austria, Finland, France, Germany, Netherlands, Norway, Portugal and Sweden.

In line with, Prostap® 3 and Prostap® SR, Prostap® 6 has been developed for use in the treatment of the following conditions:

- Metastatic prostate cancer.
- Locally advanced prostate cancer, as an alternative to surgical castration.
- As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

- As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

Type of application
This application is submitted in accordance Article 8(3) in directive 2001/83/EC.
This is a national application for a a line extension for a new strength (30mg) and a new pharmaceutical form (pre-filled syringe) of leoprorelin acetate.

For this line extension application, the applicant has submitted two studies: a phase II/III study to investigate the pharmacokinetics and pharmacodynamics of two doses (22.5mg and 30mg) of TAP 144-SR 6-Month depot; and a phase III study focusing on safety as a primary objective and efficacy as a secondary objective.

No bioequivalence studies have been submitted. Though pharmacokinetic data has been submitted no ratios have been calculated between the test and a reference product.
The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Leuprorelin acetate is well absorbed after subcutaneous injections. It binds to the luteinising hormone releasing hormone (LHRH) receptors and is rapidly degraded.
An initially high plasma level of leuprorelin acetate peaks at around 3 hours after a PROSTAP 6 subcutaneous injection, followed by a decrease to maintenance levels in 7 to 14 days.
Serum levels of leuprorelin acetate rise quickly with a subsequent decrease to a plateau within a few days. Within 1.8 hours the mean maximum serum levels of 102 ng/ml were measured. In the plateau phase detectable serum levels were found up until >26 weeks after administration. In some patients, leuprorelin acetate levels have been observed for up to 30 weeks. The maximum time to suppression of testosterone was found to be 28 days for responders and up to 35 days for non-responders.
The metabolism, distribution and excretion of leuprorelin acetate in humans have not been fully determined.

Pharmacokinetic study

The pharmacokinetics of a 22.5mg and 30mg dose of leuprorelin acetate was investigated in Study No. EC403: a randomized, open label, multicenter, parallel group Study on the pharmacokinetics and harmacodynamics of two doses (22.5 mg and 30.0 mg) of TAP-144-SR 6-Month (leuprorelin acetate) depot formulations in patients with prostatic cancer that included 63 subjects. This was a combined pharmacokinetic and efficacy study and was described as a phase 2/3 study.

Pharmacokinetic Variables
AUC(0-tlast) and Cmax were defined as primary endpoints.

Results of pharmacokinetic study
The results of the pharmacokinetic study are shown below by dose and responder status. Responders were defined as those subjects who successfully maintained testosterone suppression (i.e. without two consecutive elevations of testosterone level >50 ng/dL after the initial expected increase of testosterone levels) until 26 weeks (Visit 30) after injection of study drug.

Comparisons between responders and non-responders revealed a tendency to higher median values for Cmax, AUC(0-tlast), AUC(0-26) and AUC(0-30) in responders treated with 22.5 mg or 30mg leuprorelin.
There was no difference in tmax between responders and non-responders in the 22.5 mg group, whereas tmax was longer in responders than in non-responders in the 30 mg group.
Leuprorelin serum levels vs. time curves showed a similar course in both treatment
groups for responders with higher concentrations being seen in the 30 mg group.

Summary of the Pharmacokinetic Parameters for Leuprorelin: Cmax, tmax, AUC(0-tlast), AUC(0-26) and AUC (0-30) (FAS)

Responders

	Treatment group 22.5mg					Treatment group 30mg				
	Arith mean	SD	Geo mean	Median	N	Arith mean	SD	Geo mean	Median	N
C ($_{max}$) [pg/mL]	88557	22767	85970	87935	21	98396	29463	93664	94409	23
$t_{/(max)}$ [hrs]	1.88	0.63	1.79	2.00	21	1.94	0.56	1.87	2.00	23
AUC(0-tlast) [(pg*hrs)/mL	1819872	962341	1653317	1626206	21	1992412	766502	1856767	1881087	23
AUC(0-26) [(pg*hrs)/mL]	1811180	924039	1655560	1596494	20	1937338	729106	1812195	1850641	23
AUC(0-30) [(pg*hrs)/mL	1829776	955019	1668417	1626206	21	2001950	779969	1862434	1910426	22

Non responders

	Treatment group 22.5mg					Treatment group 30mg				
	Arith mean	SD	Geo mean	Median	N	Arith mean	SD	Geo mean	Median	N
C ($_{max}$) [pg/mL]	73202	19894	71111	63239	10	116340	43834	109117	116149	6
$t_{/(max)}$ [hrs]	2.07	1.43	1.78	1.98	10	1.36	0.64	1.21	1.38	6
AUC(0-tlast) [(pg*hrs)/mL	1391879	407379	1333954	1427480	10	1950069	839780	1779411	2024459	6
AUC(0-26) [(pg*hrs)/mL]	1424952	395552	1371339	1433299	8	1684438	545109	1616546	1902323	3
AUC(0-30) [(pg*hrs)/mL	1544147	295645	1524095	1466012	8	1715649	574752	1641966	1907699	3

IV.3 Pharmacodynamics

PROSTAP 6 contains leuprorelin acetate, a synthetic nonapeptide analogue of naturally occurring GnRH, which possesses greater potency than the natural hormone. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of testicular steroid secretion. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin acetate results in an initial increase in circulating levels of gonadotrophins, which leads to a transient increase in gonadal steroid levels.
Continued administration of leuprorelin acetate results in a decrease of gonadotrophin and sex steroid levels. In men serum testosterone levels, initially raised in response to early luteinising hormone (LH) release, fall to castrate levels in about 2-4 weeks.

Leuprorelin acetate is inactive when given orally.
A randomised, open-label, comparative multi-centre study was performed to compare the efficacy and safety of the 3.75 mg and 11.25 mg depots of leuprorelin acetate.
48% of patients included had locally advanced disease (T3N0M0), 52% of patients had metastatic disease. Mean serum testosterone level fell below the threshold for chemical castration (0.5 ng/ml) at one month of treatment, continuing to decrease thereafter and stabilising at a value below the castration threshold. The decline in serum PSA mirrored that of serum testosterone in both groups.

In an open, prospective clinical trial involving 205 patients receiving 3.75 mg leuprorelin acetate on a monthly basis as treatment for metastatic prostate cancer, the long-term efficacy and safety of leuprorelin acetate was assessed. Testosterone levels were maintained below the castrate threshold over the 63-month follow up period.
Median survival time exceeded 42.5 months for those receiving monotherapy and

30.9 months for those receiving leuprorelin acetate in combination with antiandrogens (this difference relating to baseline differences between groups).
In a meta-analysis involving primarily patients with metastatic disease, no statistically significant difference in survival was found for patients treated with LHRH analogues compared with patients treated with orchidectomy.
In another randomised, open-label, multi-centre comparative trial, leuprorelin acetate in combination with flutamide has been shown to significantly improve disease-free survival and overall survival when used as an adjuvant therapy to radiotherapy in patients with high-risk localised (T1-T2 and PSA of at least 10 ng/mL or a Gleason score of at least 7), or locally advanced (T3-T4) prostate cancer. The optimum duration of adjuvant therapy has not been established. This US study used a higher dose of leuprorelin acetate (7.5 mg/month) which is therapeutically equivalent to the European licensed dose.
The use of a LHRH agonist may be considered after prostatectomy in selected patients considered at high risk of disease progression. There are no disease-free survival data or survival data with leuprorelin acetate in this setting.

IV.4 Clinical Efficacy

Two studies were performed in patients with histologically confirmed prostate cancer of any grade or stage who had been treated with radical prostatectomy or radiotherapy. Efficacy was evaluated indirectly through the assessment of testosterone suppression. Neither study was designed primarily as an efficacy study. (For type of study and number of participants see Pharmacokinetic studies heading).

The primary objectives of Study EC403 were to show: that testosterone serum levels are suppressed to castration level (≤50ng/dL or ≤1.73 nmol/L) within 12 weeks of commencing therapy and to determine whether durability of this response can be maintained over 26 weeks; and demonstrate continuous release of leuprorelin from the depot over 26 weeks.

The primary efficacy endpoint was suppression of testosterone serum concentration to castration level (≤50 ng/dL or ≤1.73 nmol/L) within 12 weeks after commencement of therapy and maintenance of this response over a period of 26 weeks. Furthermore, the time to suppression of testosterone serum concentration to castration level was to be evaluated and testosterone and leuprorelin acetate se levels were to be correlated.

Results

All subjects (100%) in both treatment groups showed a decrease in testosterone concentration to ≤50 ng/dL within 12 weeks of the injection of study drug. Twenty-one (67.7%) subjects in the 22.5 mg and 24 (80.0%) subjects in the 30 mg treatment group maintained this suppression of testosterone until at least Week 26. This difference was not statistically significant.

Testosterone response

Suppression of testosterone ≤50 ng/dL

	Testosterone responders				Difference in rates (30 mg minus 22.5 mg)		
			95% confidence interval [%]			95% confidence interval [%]	
	N	%	lower limit	upper limit	%	lower limit	upper limit
Within 12 weeks (Visit 16)							
22.5 mg treatment group, N=31	31	100.0	98.4	100.0			
30 mg treatment group, N=30	30	100.0	98.3	100.0			
Within 12 weeks and still present after 26 weeks (Visit 30) - Responder							
22.5 mg treatment group, N=31	21	67.7	49.7	85.8			
30 mg treatment group, N=30	24	80.0	64.0	96.0	12.3	-12.8	37.3

Subject 01/610 (30 mg) excluded from the analysis.

Time to Suppression of Testosterone (FAS)

The mean time to suppression of testosterone (to below 50ng/dL) in responders was slightly longer in the 22.5 mg gı (17.1 days) than in the 30 mg treatment group (14.3 days). No difference was observed for the median time to suppres between the treatment groups.

In non-responders, there was no relevant difference in the mean time to suppression of testosterone between the treatr groups (18.9 and 18.2 days for the 22.5 mg and 30 mg groups, respectively), although the 22.5 mg group did sho slightly higher median time than subjects treated with 30 mg (21 days and 15 days, respectively).
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Responders

Time to suppression [days]	Responder definition based on 50 ng/dL (primary criterion)					
	Mean	SD	Minimum	Median	Maximum	N
22.5 mg treatment group, N=21	17.1	6.5	7.0	14.0	35.0	21
30 mg treatment group, N=24	14.3	5.9	7.0	14.0	28.0	24

Non-responders

Time to suppression [days]	Responder definition based on 50 ng/dL (primary criterion)					
	Mean	SD	Minimum	Median	Maximum	N
22.5 mg treatment group, N=10	18.9	8.8	7.0	21.0	35.0	10
30 mg treatment group, N=6	18.2	8.3	14.0	15.0	35.0	6

Study EC 404
The objectives of this study were to investigate the safety and tolerability profile of two 6-month depot (6M depot) dosages (22.5 mg and 30.0 mg leuprorelin acetate, respectively) compared to the marketed 3-month depot (3M depot) formulation (containing 11.25 mg leuprorelin acetate) over a treatment period of 12 months. In addition, the efficacy of the three treatments was to be evaluated.

This was a randomised, open-label, multinational, three-arm, parallel group, comparative, phase III study of TAP-144 SR (3M) and two dosages of TAP-144 SR (6M) in patients with prostate cancer. Patients were stratified by whether they were treatment naieve for hormone therapy or whether they had been pre-treated for up to 3 months with a GnRH/LHRH analogue and or an antiandrogen.

296 male patients aged 18 to 85 years with prostate cancer, histologically confirmed by biopsy, of any grade and st requiring chemical castration, and with a life expectancy of more than 12 months. For patients who had not received p hormone treatment testosterone and PSA at screening were to be > 150ng/dl and > 1ng/ml respectively (stratum B) pric receiving a 1month depot to ensure hormone sensitivity. For patients receiving GnRH analogue/antiandrogen treatmen < 3months (stratum A) and stratum B testosterone was to be < 80ng/dl prior to randomisation.
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Number of patients (planned, randomised and analysed):

	3M (11.25mg)	6M (22.5mg)	6M (30.0mg)	Total
Planned	50	100	100	250
Randomised	58	118	120	296
Safety analysis (ITT)	58 (58)	118 (117)	120 (120)	296 (295)

Results

The main efficacy endpoint of the study was the overall response to treatment with respect to testosterone suppression (responder was defined a subject who did not have two or more consecutive testosterone levels greater than 50ng/dL). The results are shown in the table below. Response rates were highest in the 6M depot 30mg preparation. However this difference in response rate was not statistically significant (see Table)

Table Response to treatment showing confidence intervals and comparisons of differences between treatments with their confidence intervals

	3M depot 11.25 (n=58)			6M depot 22.5 (n=117)			6M depot 30 (n=120)		
	N	%	95 % Confidence Interval	N	%	95 % Confidence Interval	N	%	95 % Confidence Interval
Responders	47	81.0	68.6 – 90.1	100	85.5	77.8 – 91.3	111	92.5	86.2 – 96.5
	3M depot 11.25 vs. 6M depot 22.5			3M depot 11.25 vs. 6M depot 30			6M depot 22.5 vs. 6M depot 30		
	Difference	95 % Confidence Interval		Difference	95 % Confidence Interval		Difference	95 % Confidence Interval	
Response	4.4 %	-8.8 – 17.7		11.5 %	-1.0 – 23.9		7.0 %	-1.8 – 15.8	

Response to treatment by time point

There were no relevant differences between the different treatment groups or strata in terms of response by time point.

Conclusions

Testosterone suppression is a key therapeutic intervention in the management of advance prostate cancer. Two other long acting leuprorelin products have been on the Irish market for a number of years. The applicant is proposing the 30mg dose for a new 6 month depot product. This product is already licensed through the national route in a number of European states.

Neither of the submitted studies was designed as an efficacy study and both are under-powered, though both are submitted to support efficacy. However both demonstrate that the 30mg and 22.5mg are successful in suppressing testosterone in a large proportion of patients. Proportions achieving suppression are higher for the 30mg dose in both studies.

However this difference is not significant in either study. The applicant has been asked to justify the reasons for choosing the 30mg dose in preference to the 22.5mg dose.

IV.5 Clinical Safety

The proportion of events considered related to study treatment was similar in the 22.5mg and 30 mg groups in study EC403. However the proportion of severe adverse events was higher in the 30 mg group (12.9% v 6.5%). Likewise the incidence of AEs considered related in study EC404 was similar across the treatment groups.

In EC403 the most frequently observed AEs were flushing, injection site erythema, injection site induration and erectile dysfunction NOS. In EC404 the most common events reported were known side-effects of LHRH analogue therapy administered by subcutaneous injection such as flushing, injection site reactions, hypertension, dizziness, sweating and nocturia; symptoms related to hormone suppression and the form of administration.

A comparison of the incidences of these events showed that dizziness, nocturia, sweating and flushing were all seen less frequently with the new 6M formulations. However, there was a dose related increase in incidence of injection site reactions with the rate of injections leading to reactions being 8.8 % and 11.8 % for the 22.5 mg and 30 mg 6M

formulations respectively, compared to 2.0 % for the 3M formulation. In addition, a small increase in incidence of hypertension with increased dose was seen.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

The device –dual chamber syringe
The dual chamber syringe has not previously been used in Ireland for the administration of Prostap products.
Dual chamber syringe (DCS) presentations of the 1-Month, 3-Month and 6-Month depot formulations of leuprorelin have been authorised and marketed in a number of countries in the EU by Takeda affiliate companies or Takeda licensees.

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Clinical Overview
An acceptable clinical overview (containing 29 references) prepared by Dr Erika Kienle was submitted which summarized the results of the two submitted studies along with providing information on product development, an overview of the the biopharmaceutics and clinical pharmacology.

IV.6 Discussion on the clinical aspects

Neither of the submitted studies was designed as an efficacy study and both are under-powered, though both are submitted to support efficacy. However both demonstrate that the 30mg and 22.5mg are successful in suppressing testosterone in a large proportion of patients. Proportions achieving suppression are higher for the 30mg dose in both studies. However this difference is not significant in either study. The applicant has been asked to justify the reasons for choosing the 30mg dose in preference to the 22.5mg dose.
The applicant justified the choice of dose on the following basis. In study EC404 using the criteria of achieving a 90% response rate, equivalent to that attained with the gold standard therapy of surgery (orchidectomy), as a mean value this was achieved (>90% responder) for the 30 mg dose, but not the 22.5 mg dose. Although the lower confidence interval (CI) is below 90% this should be expected as it is usual with other existing marketed products and also with orchidectomy itself.
In study EC403, patients showed a tendency to a shorter time to suppression of testosterone to castration levels in the 30 mg group (mean values: responders, 14.3 days; non-responders, 18.2 days) compared to the 22.5 mg group (mean values: responders, 17.1 days; non-responders, 18.9 days). Further analysis suggested a tendency in the 30 mg group to an earlier occurrence of testosterone suppression (100% at week 4 in the 30 mg group versus 100% at week 5 in the 22.5 mg group), a more reliable pattern of maintenance and a longer duration compared to the 22.5 mg group.

The 30 mg dosage strength is therefore proposed for approval as the recommended therapeutic dose of leuprorelin acetate due to the more favourable efficacy profile associated with the formulation, based on the results of the EC 404 study, albeit that efficacy was not the primary endpoint of the study.
However, in this study, the difference in response rate between the two doses of the 6M depot was 7.0% in favour of the 6M 30 mg depot (95% CI: -1.8%, 15.8%), with more confirmed testosterone elevations (escapes, 14.5% versus 7.5%) in the 6M 22.5 mg group. In addition, the primary endpoint of safety confirmed a comparable safety profile between the two doses of the 6M depot.

The above explanation was accepted given that the 30mg dose is already licensed in a number of European states.

SPC
The submitted SPC was broadly in line with the SPCs for Prostap SR 3.75mg and Prostap 3 11.25mg. The applicant was asked to update sections 4.3 and 4.8 to bring the Irish SPC in line with the German SPC and to add a warning to

4.4 regarding osteoporosis to bring it in line with the PIL.

PIL
A user testing report was submitted with the PIL (See full user test report). This was acceptable. The applicant was asked to move a warning in section 2 regarding orchidectomy or previous non-response to testosterone supressors from 'Take special care' to 'Do not take'.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation

Testosterone suppression is a key therapeutic intervention in the management of advance prostate cancer. Two other long acting leuprorelin products have been on the Irish market for a number of years. The applicant is proposing the 30mg dose for a new 6 month depot product. This product is already licensed through the national route in a number of European states.

Neither of the submitted studies was designed as an efficacy study and both are under-powered, though both are submitted to support efficacy. However both demonstrate that the 30mg and 22.5mg are successful in suppressing testosterone in a large proportion of patients. Proportions achieving suppression are higher for the 30mg dose in both studies. However this difference is not significant in either study. The applicant has been asked to justify the reasons for choosing the 30mg dose in preference to the 22.5mg dose. The applicant's justification has been accepted by the assessor. The applicant has demonstrated that testosterone suppression achieved by the 30mg 6 month depot preparation is at least equivalent to that demonstrated by the 11.25mg 3 month depot preparation.
No new safety issues pertinent to the 6 month depot product were identified in the clinical trials submitted by the applicant.

Given the evidence regarding efficacy and the fact that no new major safety issues have been identified in the trials the assessor considers that the benefit risk balance is positive.

The SPC is consistent with that of other Prostap products licensed in Ireland. However the applicant was requested to update the SPC in line with the German SPC.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted, considered that Prostap 6 (leuoprorelin acetate) Advanced System 30mg Powder and Solvent for Prolonged-Release Suspension for Injection demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI REVISION DATE

June 2018