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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Decapepty; 6-month 22.5 mg Powder and Solvent for Prolonged-Release Suspension for Injection

Triptorelin Pamoate

PA 0869/003/003

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Decapeptyl 6-month, 22.5 mg Powder and solvent for prolonged-release, from Ipsen Pharmaceuticals Ltd on 8th April 2011 for Decapeptyl 6 Month is indicated for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer.

This application for a marketing authorisation was submitted as a line extension to the existing marketing authorisation Decapeptyl 11.25 mg, powder and solvent for suspension for injection PA 869/3/2. This application is submitted in accordance with Article 8(3) of 2001/83/EC as amended.

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

Name of the product	Decapeptyl 6-month 22.5 mg Powder and solvent for prolonged-release suspension for injection
Name(s) of the active substance(s) (INN)	TRIPTORELIN PAMOATE
Pharmacotherapeutic classification (ATC code)	L02AE04
Pharmaceutical form and strength(s)	22.5 mg Powder and solvent for prolonged-release suspension for injection

II QUALITY ASPECTS

II.1. Introduction

This application is for Decapeptyl 6-month 22.5 mg Powder and Solvent for prolonged-release Suspension for Injection.

II.2 Drug substance

The active substance is Triptorelin pamoate, an established active substance not described in the European/British Pharmacopoeia. It 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

Powder for prolonged-release suspension for injection

P.1 Composition

The drug product is a sterile, lyophilized, biodegradable microgranules formulation supplied as a single-dose vial containing triptorelin embonate (28 mg as the peptide base), poly (DL-lactide co-glycolide) mannitol, carmellose sodium and polysorbate 80. When 2 mL sterile water for injection, is added to the vial containing triptorelin embonate and mixed, a suspension is formed which is intended as an intramuscular injection to be administered every 24 weeks.

Triptorelin embonate 22.5 mg is available in 1 packaging configuration: Triptorelin embonate 22.5 mg vial plus a separate colourless neutral glass ampoules, type I, Eur Ph., with a nominal volume of 2 ml of sterile water for injection.

P.2 Pharmaceutical Development

The product is a powder for prolonged-release suspension for injection and its development is adequately described in accordance with the relevant European guidelines. Formulation development was based on the knowledge and experience acquired with the approved triptorelin 3mg (1-month sustained release) and triptorelin pamoate 11.25 mg (3-month sustained release) formulations.

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/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

The excipients carmellose sodium, mannitol, nitrogen, polysorbate 80 and water for injection will meet the requirements of the current edition of the European Pharmacopoeia. Poly (d, l-lactide-co-glycolide) is not described in a European Pharmacopoeia. Poly (d, l-lactide-co-glycolide) specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the parenteral preparations, 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

6 ml septum vial (type I glass) with bromobutyl stopper and aluminium flip-off cap.

Evidence has been provided that the packaging complies with the current European requirements.

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. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC).

The powder should be suspended immediately before use and only the solvent supplied should be used. Once open the product should be used immediately (see the SPC for further information).

Solvent for prolonged-release suspension for injection

P.1 Composition
The drug product is supplied with solvent. The solvent is water for injection (Ph. Eur.). The container is colourless neutral glass ampoules, type I, Ph. Eur. with a nominal volume of 2 ml.

P.2 Pharmaceutical Development

Not applicable.

P.3 Manufacture of the Product

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

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

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

Not applicable.

P.5 Control of Finished Product (Solvent)

The Finished Product Specification for Water for Injections is based on the corresponding European Pharmacopoeia monograph. All control methods are in line with the monograph and the tests and control limits are considered appropriate for this type of product.

Batch analytical data for a number of batches have been provided.

P.6 Packaging material

Ampoule (type I glass) containing 2 ml of sterile solvent for suspension.

Evidence has been provided that the packaging complies with the current European requirements.

P.7 Stability of the Finished Product

Stability data on the solvent in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the solvent as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC). The powder should be suspended immediately before use and only the solvent supplied should be used. Once open the product should be used immediately (see the SPC for further information).

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 Decapeptyl 6-month 22.5 mg Powder and Solvent for prolonged-release Suspension for Injection.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European market for 25 years (since 1986 in France). Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

IV CLINICAL ASPECTS

IV.1 Introduction

Decapeptyl 6-month 22.5 mg Powder and Solvent for Suspension for Injection is indicated for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer. Efficacy and safety of the 6 month depot formulation are assessed also taking into account the data provided in the dossier of the 3-month depot formulation of triptorelin.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted. The applicant supports the application for a marketing authorisation for Decapeptyl 22.5 mg with the results of 6 completed clinical trials, only two of which used the formulation to be marketed (see Table 1).

- DEB-TRI6M-301: pivotal trial, the recommended dose (22.5 mg for 6 month (24 weeks) formulation) in two subsequent administrations (n=120).
- DEB-TRI6M-201, arm A as pilot study for DEB-TRI6M-301 (n=8).

Table1. Overview of DEB-TRI6M-301 (pivotal) and DEB-TRI6M-201 (pilot) studies.

Study ID	Number of study centers, location	Study start, enrollment status, date enrollment total / goal	Design, control type	Study and control drugs, dose, route and regimen	Study objective	Number of subjects by arm treated / completed	Duration of treatment	Gender M/F, mean age (range)	Diagnosis,Inclusion criteria	Primary end point(s)
DEB-TRI6M-301	13 sites South Africa	Started 10 Jul 2006; completed 14 Aug 2007 120 / 120	Open-label uncontrolled	22.5 mg IM q24w x 2	Efficacy and safety (pivotal study)	120 / 115	48 weeks	120 / 0 71 y (51-93)	Locally advanced or metatstatic, hormone dependentp rostate cancer	Achievement of castration at D29; maintenance of castration D57 to D337
DEB-TRI6M-201	2 sites Bulgaria	Started 25 May 2005; completed 27 Feb 2006 24 / 24	Open-label, parallel group	22.5 mg IM q24w x 1	Efficacy and safety (pilot study)	8 / 8 arm A*	24 weeks	8 / 0 71 y (59-80) arm A*	Locally advanced or metatstatic, hormone dependentp rostate cancer	Achievement of castration at D29; maintenance of castration D57 to D169

* formulation identical to triptorelin 6-month formulation

Four other trials were discussed in the application (Table 2 and 3).

Table 2 Description of Clinical Efficacy Studies of the 1- and 3-Month Ipsen Formulations

Study ID	Study location	Study date	Study design	Study treatment, dose, route, regimen	Study objectives	Number of subjects by arm	Duration of treatment	Mean age ± SD (range)	Diagnosis, inclusion criteria	Primary end points
UK DCP 94-090	UK	1995	Open, multicenter, randomized, asymetric study	Triptorelin PR 11.25 mg One intramuscular injection of 11.25 mg Triptorelin Triptorelin PR 3.75 mg Three intramuscular injections of 3.75 mg Triptorelin at intervals of 28 days	Pharmacokinetics, pharmacodynamics and bioequivalence of 2 sustained-release formulations of triptorelin	Triptorelin 11.25 mg: 41 Triptorelin 3.75 mg: 22	3 months 3 months	72.6 ± 8.4 years (53 – 88) n = 39* 70.2 ± 8.0 years (54 – 88) n = 20*	Prostate carcinoma suitable for hormonal therapy	Testosterone level on the final visit at Month 3 Time to castrate level
UK DCP 94-094	UK	1995	Open, multicenter, long-term follow-up of study UK DCP 94-090	Triptorelin PR 11.25 mg One intramuscular injection of 11.25 mg Triptorelin every 3 months	Pharmacodynamic parameters during long-term (3 to 9 months) treatment	49	3 to 9 months	Same age range as in Study UK DCP 94-090	Prostate carcinoma suitable for hormonal therapy	Testosterone levels

* Population evaluable for efficacy (Per Protocol)

Table 3 Description of Clinical Efficacy Study of 1- and 3-Month Debiopharm Formulations

Study ID	Number of study centers, location	Study start, enrollment status, date, enrollment total / goal	Design, control type	Study and control drugs, dose, route and regimen	Study objective	Number of subjects by arm treated / completed	Duration of treatment	Gender M/F, mean age (range)	Diagnosis, inclusion criteria	Primary end point(s)
DEB-96-TRI-01, 1st phase	21 sites South Africa	Started 27 Jan 1997; completed 04 Sep 1998 346 / 350	Randomized, open-label, parallel group, active-controlled	11.25mg IM q12w x 3 3.75 mg IM q4w x 9	Efficacy and safety	174 / 148 172 / 144	36 weeks	174 / 0 70y (48-96) 172 / 0 71y (45-89)	Advanced prostate cancer	Achievement of castration at D29; maintenance of castration D57 to D253
DEB-96-TRI-01, 2nd phase	29 sites South Africa	Started 09 Jan 1998; completed 11 Feb 1999 284 / 280	Randomized, open-label, parallel group, active-controlled	3.75mg IM q4w x 9 Leuprolide 7.5mg IM q4w x 9	Efficacy and safety; compare w/ competitive product	140 / 120 144 / 120	36 weeks	141 / 0 70.5y (47-88) 144 / 0 71.5y (49-89)	Advanced prostate cancer	Achievement of castration at D29; maintenance of castration D57 to D253

(synopsis in 2.7.6)

IV.2 Pharmacokinetics

The applicant has compared the pharmacokinetic parameters from the 6-month formulation phase 3 pivotal study (DEB-TRI6M-301) with the data from the clinical studies with Ipsen 3-month formulation (UK DCP 94-090 and 52014ST 8077) and the Debiopharm 1- and 3-month formulations.
While pharmacokinetic characteristics of the three formulations differ slightly with respect to the values of C_{max} and AUC, these differences in PK parameters in depot formulations are expected and do not raise safety concerns (Table 4).

Distribution and elimination have already been established for the approved 3 month formulation. There is no reason to assume a different behaviour for triptorelin released from the 6 month formulation.

Table 4 Triptorelin Pharmacokinetic variables

Triptorelin Pharmacokinetic Variables for the 6-Month Formulation				
Formulation [Study]	**N**	**Geometric Mean (range) C_{max} after 1st injection (ng/mL)**	**Median (range) t_{max} after 1st injection (hours)**	**Geometric Mean (range) AUC over 6 months (days•ng/mL)**
6-month [DEB-TRI6M-301 pivotal study]	15	40.0 (22.2-76.8)	3 (2-12)	111.5 (52.2-177.4) ($AUC_{169-337d}$)

Triptorelin Pharmacokinetic Variables for the 3-Month Ipsen Formulation				
Formulation [Study]	N	**Mean (range) C_{max} after 1 injection (ng/mL)**	**Mean (range) t_{max} after 1 injecti**	**Mean (range) AUC_{0-91} (days•ng/mL)**
3-month [UK DCP 94-090]	5	21.3 (11.7-37.1)	3.6 (2.0-4.6)	18.4 (10.6-28.7)
3-month [52014 ST 8077]	14	35.7 (9.1-70.7)	2.6 (1.0-4.1)	37.2 (17.1-85.0)

Triptorelin Pharmacokinetic Variables for 3-Month and 1-Month Debiopharm Formulations				
Formulation [Study]	N	**Geometric Mean (range) C_{max} after 1st injection (ng/mL)**	**Median (range) t_{max} after 1st injection (hours)**	**Geometric Mean (range) AUC over 6 months (days•ng/mL)**
3-month [DEB-96-TRI-01] 1st phase, pivotal study	13	35.8 (16.5-57.4)	2 (1-4)	202.3 (117.6-325.2) ($AUC_{169-253d}$ x2)
1-month [DEB-96-TRI-01] 1st phase, supportive study	14	15.6 (9.1-25.2)	2 (2-4)	197.9 (101.8-452.6) ($AUC_{169-253d}$ x2)

IV.3 Pharmacodynamics

The pharmacodynamic action of triptorelin on testosterone suppression is an accepted surrogate parameter for determining efficacy of gonadotrophin releasing hormone (GnRH) agonists and the castration level was defined according to the internationally accepted cut-off level of testosterone serum levels ≤1.735 nmol/l. Despite the different initial triptorelin exposures (Cmax) with the triptorelin 1-, 3-, and 6-month formulations all formulations showed comparable mean testosterone, C_{max} and t_{max} following the first injection. Comparable geometric mean time to castration was obtained across all studies (Table 5).

Table 5 Triptorelin Pharmacodynamic variables

Testosterone Pharmacodynamic Variables for the 6-Month Formulation				
Formulation [Study]	N	**Geometric Mean (range) C_{max} after 1st injection (ng/mL)**	**Median (range) t_{max} after 1st injection (days)**	**Geometric Mean Time to castration (days)**

6-month [DEB-TRI6M-301 pivotal study]	15	25.8 (14.1-49.2)	3 (2-5)	18.8 (12.8-24.9)
Testosterone Pharmacodynamic Variables for the 1- and 3-Month Ipsen Formulations				
Formulation [Study]	N	**Mean C_{max} after 1st injection ng/mL)**	**Mean t_{max} after 1st injection (days)**	**Mean (range) Time to Castration (days)**
3-month [UK DCP 94-090]	41	30.5	2	16.7 (9.1-33.3)
3-month [52014 ST 8077]	14	28.2	2.6	22.2 (13.1-32.1)
1-month [UK DCP 94-090]	22	30.4	2	15.6 (9.4-21.4)
Testosterone Pharmacodynamic Variables for 3-Month and 1-Month Debiopharm Formulations				
Formulation [Study]	N	**Geometric Mean (range) C_{max} after 1st injection (ng/mL)**	**Median (range) t_{max} after 1st injection (days)**	**Geometric Mean Time to Castration (days)**
3-month [DEB-96-TRI-01] 1st phase , pivotal study	14	26.0 (16.9-41.4)	2 (1-4)	not available
1-month [DEB-96-TRI-01] 1st phase, supportive study	15	21.4 (5.5-37.5)	4 (1-6)	not available

Triptorelin Pharmacokinetic/Pharmacodynamic Relationship

The triptorelin PK/PD relationship is highly non-linear (on-off response) and time-dependent due to the desensitization of the pituitary.
Once the desensitization of the pituitary GnRH receptors has been achieved (and castration induced), the down-regulation of the GnRH receptors and castration are maintained with very low triptorelin levels.

IV.4 Clinical Efficacy

The applicant submitted the pivotal clinical trial DEB-TRI6M-301 in support of the application for marketing authorisation of the line extension for triptorelin 22.5mg.

DEB-TRI6M-301 was an uncontrolled trial with 120 patients with advanced prostate cancer. The primary objective of the study was to assess the percentages of patients with locally advanced or metastatic, hormone-dependent prostate cancer who achieved castrate levels of testosterone (≤1.735 nmol/L) 28 days after the first injection of study drug. 97.5% of the patients in the intent-to treat (ITT) population achieved castrate levels of testosterone on Day 29, and 93.0% of the patients maintained these levels from Day 57 to Day 337. Following the second injection of study drug, 98% (117/119) of patients showed an absence of luteinising hormone (LH) stimulation. The mean percentage prostate specific antigen (PSA) decrease from baseline to end of treatment was 82.3% in the ITT population. Ninety-three patients in the ITT population (80.9%) had normal PSA values (<4 µg/L) at D337. All efficacy assessments for the 6-month formulation are similar to those for the 1-month and 3-month formulations. (Table 6 and 7).

Age, body mass index (BMI) and ethnicity had no significant effect on the rate of castration at Day 29 and maintenance of castration from Days 57-336. No tolerance effects to triptorelin 22.5 mg, (indicated by escape from castration) were observed in the pivotal clinical trial involving 120 patients treated over 48 weeks.
The proportion of patients maintaining castration following administration of 22.5 mg was comparable to the 1 and 3 month authorised formulations.

Table 6 Key Efficacy Results from the Pivotal Study with the 6-Month Formulation (ITT)

Efficacy End point	DEB-TRI6M-301 6-month
Patients castrated on Day 29, 28 days after injection % (n/N) (95% confidence interval)	**97.5% (117/120) (92.9%-99.5%)**
Patients maintaining castration from Days 57-337, % (n/N) (95% confidence interval)	**93.0% (107/115)[a] (86.8%-97.0%)**
Patients maintaining castration from Days 57-253, % (n/N) (95% confidence interval)	94.1%[b] (89.9%-98.4%) Months 2-9
Patients with ≤1.0 IU/L increase in LH from 0-2h after the 2nd injection, % (n/N)	Day 169: 98.3% (117/119)
Patients showing "acute-on-chronic" phenomenon, i.e., escape from castration 48h after the second injection, % (n/N)	1.7% (1/59)[c]
Group median change in PSA from baseline to Week 24	96.9%
Group median change in PSA from baseline to end of study	96.4% (Week 48)

[a] Calculation excludes 5 patients who discontinued the study due to non-drug-related reasons (2 patients who died due to disease progression; 1 patient who died of myocardial infarction; 1 patient lost to follow-up after Day 176; and 1 patient who withdrew consent after Day 281)
[b] Cumulative maintenance of castration was calculated using a survival analysis (Kaplan-Meier) technique. Results presented for maintenance for Months 2-9 reflect 2 injections of the 6-month formulation (partially), 3 injections of the 3-month formulation, and 9 injections of the 1-month formulation.
[c] Assessed in a subset of 60 patients; calculation excludes 1 patient who never achieved castration.

Table 7 Key Efficacy Results from Supportive Studies of Triptorelin 1- and 3-Month Debiopharm Formulations (ITT)

Efficacy End point	DEB-96-TRI-01 1st phase 3-month	DEB-96-TRI-01 1st phase 1-month
Patients castrated on Day 29, 28 days after injection % (n/N) (95% confidence interval)	**97.7% (167/171) (94.1%-99.4%)**	**92.7% (152/164) (87.6%-96.2%)**
Patients maintaining castration from Days 57-337, % (n/N) (95% confidence interval)	**not available**	**not available**
Patients maintaining castration from Days 57-253, % (95% confidence interval)	94.4%[a] (90.9%-98.0%) Months 2-9	94.2%[a] (90.6%-97.9%) Months 2-9
Patients with ≤1.0 IU/L increase in LH from 0-2h after the 2nd injection, % (n/N)	Day 85: 92.7% (153/165) Day 169: 91.7% (143/156)	Day 85: 97.4% (152/156) Day 169: 98.0 (146/149)
Patients showing "acute-on-chronic" phenomenon, i.e., escape from castration 48h after the second injection, % (n/N)	0% (0/20)[b]	0% (0/14)[c]
Group median change in PSA from baseline to Week 24	95.8%	97.0%
Group median change in PSA from baseline to end of study	96.8% (Week 36)	97.6% (Week 36)

[a] Cumulative maintenance of castration was calculated using a survival analysis (Kaplan-Meier) technique. Results presented for maintenance for Months 2-9 reflect 2 injections of the 6-month formulation (partially), 3 injections of the 3-month formulation, and 9 injections of the 1-month formulation.

[b] Assessed in a subset of 60 patients; calculation excludes 1 patient who never achieved castration.

[c] Assessed in a subset of 13 patients in Study DEB-96-TRI-01, 2nd phase.

Conclusion: The 6-month formulation is as effective as the 1- and 3-month formulations in treating patients with locally advanced or metastatic, hormone-dependent prostate cancer, with the advantage of less frequent injections than with the 1-month and 3-month formulations.

IV.5 Clinical Safety

IV.5.1 Overview of safety

Triptorelin has been authorised for use in Ireland since 1991. The safety profile of triptorelin and the pharmacodynamic consequences of androgen ablation are well described.

The safety profile for triptorelin 6-month is based on the safety data from the non-comparative pivotal study DEB-TRI6M-301, involving 120 patients exposed to the study drug for 48 weeks. In the pivotal study of the triptorelin 6-month formulation, 97.5% (117/120) of patients were exposed to 48 weeks of treatment with a cumulative triptorelin dose of 45.0 mg.

The most common adverse events are related to the suppression of testosterone levels, which is due to the intended pharmacological action of the drug. In the pivotal study of the 6-month formulation, 95.8% (115/120) of the patients reported at least one treatment-emergent adverse event (TEAE). The majority of these TEAEs were mild or moderate in severity: The most frequently reported TEAEs, occurring in ≥10% of patients, were hot flushes (72.5%), influenza (15.8%), hypertension (14.2%), back pain (10.8%), and erectile dysfunction (10.0%). The 6-month formulation was well tolerated locally.

Clinical data generated by the pivotal study DEB-TRI6M-301 study suggests that the 6-month formulation has a comparable safety profile to the 1- and 3-month formulations.

As the pharmacokinetic/pharmacodynamic relationship for triptorelin is non-linear and the safety margin of triptorelin is large, no dose adjustment is required for renal or liver impairment in spite of an increased exposure in patients with severe renal or hepatic impairment.

A brief overview of the post-marketing surveillance of triptorelin between 1987 through March 2008 is provided as part of the application. No new trend in the safety profile of triptorelin in patients with advanced prostate cancer was identified during this review.

There have been literature reports indicating that longterm GnRH agonist treatment may also lead to metabolic changes, such as increased body weight, fasting blood sugar and serum concentrations of total cholesterol, which could increase the risk of diabetes mellitus and cardiovascular disease. Section 4.4 of the SPC was updated with warnings regarding necessity of increased monitoring of patients at risk for effects on blood glucose, diabetes, cardiac disease in line with other GnRH (ant) agonists.

Conclusion: The overall safety profile of the triptorelin 6-month formulation is comparable to that of the approved triptorelin 1 and 3 month formulations and other sustained release GnRH agonists.

IV.5.2 Risk Management Plan

Safety Specification

Limitations of the human safety data base.

Clinical trials exposure

One thousand two hundred and twenty-four (1224) men in total (prostate cancer and healthy volunteers) have been treated with different salts of triptorelin in the clinical trials. Of these 506 patients (41.3 %) were treated for 9 months, 117 patients (9.5%) for 12 months and 156 patients (12.7%) for more than one year. One hundred and fifty-four (154) men have been exposed to the 6-month formulation. Of these 117 patients were treated for 12 months.

Post marketing exposure.

The cumulative worldwide patient exposure for all triptorelin formulations and all indications is estimated >2 million treatment years from 1986 through March 2008.

Population not studied in the pre-authorisation phase.

Children or pregnant or lactating women were not studied since triptorelin pamoate 6-month formulation is not indicated for use in this population.

Adverse events/Adverse drug reaction.
The overall safety profile of the triptorelin 6-month formulation is comparable to that of the approved triptorelin 1- and 3-month formulations and other registered sustained release GnRH agonists. The most frequently observed drug related adverse events identified in the pivotal 6-month formulation study (hot flushes (72%), erectile dysfunction (10%) and testicular atrophy (7.5%)), are directly related to the main pharmacologic effect of the drug, i.e. decrease in testosterone levels.

Long term safety.

Some evidence in the literature suggests that GnRH agonist treatment may also lead to metabolic changes, such as increased body weight, fasting blood sugar and serum concentrations of total cholesterol, which could increase the risk of diabetes mellitus and cardiovascular disease.
Over 22 years experience with different triptorelin salts and formulations the MAA received notice of 489

spontaneously reported serious adverse events (SAEs) associated with more than two million treatment years cumulative exposure to various triptorelin formulations. Of the 132 (27%) SAEs reported for prostate cancer patients receiving any triptorelin formulation, there were 3 (2%) reports of hypertension, 1(1%) hypertensive crisis, 1(1%) myocardial infarction, 3(2%) cerebrovascular accidents, 3(2%) thrombosis and no cases of diabetes mellitus or hyperglycemia.

Details of important identified and potential risks.

The marketing authorisation holder has identified bone loss and metabolic changes as potential risks:
Gonadotrophin-releasing hormone agonists (GnRH agonists) are known to decrease bone mineral density and increase fracture risk due to the induced hypogonadism. Since triptorelin and the other GnRH analogues produce castrate levels of testosterone, longterm use may produce effects on bone similar to those of orchidectomy.
GnRH agonist treatment may also lead to metabolic changes, such as increased body weight, fasting blood sugar and serum concentrations of total cholesterol, which could increase the risk of diabetes mellitus and cardiovascular disease.
Both risks are included in sections 4.4 and 4.8 of the SmPC. Patients at high risk of metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.
Section 4.4 contains the following warning regarding the risk of metabolic or cardiovascular disease.
“In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk of metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.”

The following statement is included in section 4.8 regarding bone loss. “The use of synthetic GnRH agonists to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture”.

Epidemiology of identified or potential risks in target population when unexposed to the product.

A prospective study comparing men receiving androgen deprivation therapy (ADT) to age matched controls (including prostate cancer patients who had completed primary therapy without evidence of disease progression, but also patients with other urologic conditions) for 2 years found greater rates of bone mineral density (BMD) loss in men receiving ADT than men in the control group.
The 2-year BMD loss (mean ± standard error) in the control group was at the distal forearm -4.4 ± 0.3 % (vs. -9.4 ± 1.0 % in the ADT treated patients), at the femoral neck 0.6 ± 0.5 % (vs. -1.9± 0.7 %), in total hip 0.8 ± 0.5 % (vs. -1.5 ± 1.0 %), at trochanter -0.1 ± 0.5 % (vs. -2.0 ± 1.3 %), in the lumbar spine 1.1 ± 0.6 % (vs. -0.2 ± 0.8 %) (20).

A recent observational study of a population-based cohort of 73,196 patients estimated in prostate cancer patients under GnRH agonist treatment and without treatment the unadjusted rates per 1,000 person-years for developing diabetes, coronary heart disease, myocardial infarction, or sudden death.GnRH use was associated with increased risk of diabetes (adjusted hazard ratio [HR] 1.44, p<0.001), coronary heart disease (adjusted HR 1.16, p=0.004), myocardial infarction (HR 1.11, p=0.03) and sudden cardiac death (HR 1.16, p=0.004).

Identified and potential interactions

Drug Drug Interactions:
No specific studies were conducted to assess potential drug-drug interactions. Hepatic microsomal enzymes are considered unlikely to be involved in triptorelin metabolism.

Potential for off-label use.

Decapeptyl 6-month 22.5 mg is intended to be used in patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer. The currently authorized 1 and 3 month formulations in Ireland are indicated for use in women and/or children: in vitro fertilisation, endometriosis, uterine fibromyoma, precocious puberty/or where a decrease of sex hormones is indicated and where only a shorter acting formulation is approved so far. Cases of off label

use will be reported in the PSURs.
Section 4.2 includes the statements that "Decapeptyl 6 Month must be administered under the supervision of a physician. Safety and efficacy of Decapeptyl 6Month has not been established in neonates, infants, children and adolescents, therefore Decapeptyl 6 Month is not Indicated for the use in these populations. Decapeptyl 6 Month is not indicated for use in females."

IV.5.3 Pharmacovigilance Plan

The identified risks bone loss and metabolic changes are addressed by routine pharmacovigilance activities and will be evaluated in the PSUR.

Risk Minimisation activities.
Routine risk minimization activities are considered sufficient for identified safety concerns. No additional risk minimization measures are planned.

IV.6 Discussion on the clinical aspects

Data from the Phase 3 Study [DEB-TRI6M-301] in 120 patients with locally advanced or metastatic, hormone-dependent prostate cancer demonstrate that the triptorelin pamoate 6-month formulation is an effective agent for inducing and maintaining chemical castration for the treatment of advanced prostate cancer over a 6-month period. Clinical data generated from the Phase 3 study suggests that the 6-month formulation has a comparable safety profile to marketed 1- and 3-month formulations, with the most common adverse events related to the suppression of testosterone levels, which is due to the intended pharmacological action of the drug.

V OVERALL CONCLUSIONS

Data for this 6-month depot formulation were submitted as a line extension to the authorised 3-month depot formulation. These data show that Decapeptyl 6-month 22.5 mg is as effective as 3-month formulations to treat patients with locally advanced or metastatic, hormone-dependent prostate cancer, with the advantage of less frequent injections than the 3-month formulations.

The safety profile of triptorelin and the pharmacodynamic consequences of androgen ablation are well known. The pharmacokinetic/pharmacodynamic relationship for triptorelin is non-linear and the safety margin of triptorelin is large. No dose adjustment is required for organ impairment in spite of an increase of exposure in patients with severe renal or hepatic impairment. Local tolerance of the 6-month depot formulation is good and no drug hypersensitivity reactions were noted. The majority of AE and TEAEs related to triptorelin treatment are well described and can be attributed to its pharmacodynamic action. Long-term androgen deprivation in the population indicated for use may be associated with treatment-related osteoporosis, diabetes, and cardiovascular disease.

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 Decapeptyl 6-month 22.5 mg Powder and Solvent for Suspension for Injection demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.