Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection (triptorelin pamoate)

UK Licence No: PL 34926/0019

Ipsen Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection
(triptorelin pamoate)

This is a summary of the Public Assessment Report (PAR) for Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection (PL 34926/0019). This medicinal product will be referred to as Decapeptyl SR 11.25 mg in the remainder of this lay summary for ease of reading.

This summary explains how the application for Decapeptyl SR 11.25 mg was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Decapeptyl SR 11.25 mg.

For practical information about using Decapeptyl SR 11.25 mg, patients should read the package leaflet or contact their doctor or pharmacist.

What is Decapeptyl SR 11.25 mg and what is it used for?
Decapeptyl SR 11.25 mg contains the active ingredient triptorelin as triptorelin pamoate. Triptorelin belongs to a group of medicines called gonadotropin releasing hormone (GnRH) agonists. Triptorelin is similar to the gonadotropin releasing hormone which occurs naturally in your body.

Decapeptyl SR 11.25 mg has three different uses:

- In men, Decapeptyl SR 11.25 mg can be used to treat prostate cancer.
- In women, Decapeptyl SR 11.25 mg is used to treat endometriosis – a condition in which the tissue that normally lines the uterus (endometrium) grows in other places.
- In children, Decapeptyl SR 11.25 mg is used to treat puberty that occurs at a very young age (precocious puberty).

How does Decapeptyl SR 11.25 mg work?
In men, triptorelin lowers the levels of the hormone testosterone.

In women, triptorelin reduces oestrogen levels.

How is Decapeptyl SR 11.25 mg used?
The package leaflet has instructions on how to prepare the injection, but this will usually be done by a doctor or nurse.Decapeptyl SR 11.25 mg is injected into a muscle, usually the patient's bottom, by a doctor or nurse.

For men, the patient will normally receive an injection once every 3 months.

For women, the patient will normally receive two injections in total, the second one 3 months after the first. Each injection will be given in the first 5 days of the patient's period.

Children
The patient will normally receive an injection once every 3 months.

The patient's doctor will decide when treatment should be stopped (normally when the patient is about 12 years old, if female, or about 13-14 years old, if male).

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

What benefits of Decapeptyl SR 11.25 mg have been shown in studies?
Triptorelin has been available in the EU for many years for the treatment of the above conditions, and has been shown to be suitably effective and safe. Additional clinical studies have been provided to show that the effects seen with triptorelin are also seen with triptorelin pamoate.

What are the possible side effects of Decapeptyl SR 11.25 mg?
For information about side effects that may occur when using Decapeptyl SR 11.25 mg, please refer to Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why was Decapeptyl SR 11.25 mg approved?
The Medicines and Healthcare products Regulatory Agency decided that the benefits of Decapeptyl SR 11.25 mg outweigh the risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Decapeptyl SR 11.25 mg?
A Risk Management Plan (RMP) has been developed to ensure that Decapeptyl SR 11.25 mg is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Decapeptyl SR 11.25 mg
A Marketing Authorisation was granted in the UK on 6 June 2017.

The full PAR for Decapeptyl SR 11.25 mg follows this summary. For more information about treatment with Decapeptyl SR 11.25 mg read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2017.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Ipsen Limited a Marketing Authorisation for the medicinal product Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection on 6 June 2017. The product is a Prescription-Only Medicine (legal status POM) indicated for the:

- Treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration.
- Treatment of metastatic prostate cancer.
- As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.
- As neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.
- As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.
- Treatment of endometriosis.
- Treatment of precocious puberty (onset before 8 years in girls and 10 years in boys).

This is a national Article 8(3) application for Decapeptyl SR 11.25 mg Powder for suspension for injection, containing the active substance triptorelin pamoate. This application is a line extension to the existing product Decapeptyl SR 11.25 mg Powder for suspension for injection (PL 34926/0003), which was authorised in the UK in 2002 and contains the active substance triptorelin acetate. Triptorelin is a synthetic decapeptide. It is an analogue of natural gonadotrophin releasing hormone (GnRH), and is characterised principally by the replacement of the L-glycine in the six position by a D-tryptophan. Both the 11.25 mg acetate and 11.25 mg pamoate formulations are prolonged release, and are designed to release the active substance over a period of 3 months.

No new non-clinical studies were conducted. This is acceptable as the pamoate salt of triptorelin has been used clinically in the EU for many years. Clinical data have been submitted to support this application, showing that the pharmacodynamics and efficacy of this product can be considered the same as those for Decapeptyl SR 11.25 mg Powder for suspension for injection (PL 34926/0003). Bioequivalence to the approved 11.25 mg acetate formulation is not claimed. Instead, a therapeutic equivalence approach is used, based on pharmacodynamic endpoints.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application, and these are satisfactory.

II QUALITY ASPECTS

II.1 Introduction

Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection contains 15.00 mg of triptorelin pamoate.

The other ingredients in the powder consist of excipients, namely D,L lactide-glycolide copolymer, mannitol, carmellose sodium and polysorbate 80. The solvent (suspension) consists of the excipients water for injection and mannitol.

The finished product consists of:

- a powder, contained in a Type I 4ml glass vial with an elastomer stopper and an aluminium cap
- a suspension, contained in a Type I 3ml glass ampoule.

Both the vial and ampoule are boxed with a syringe and two needles.

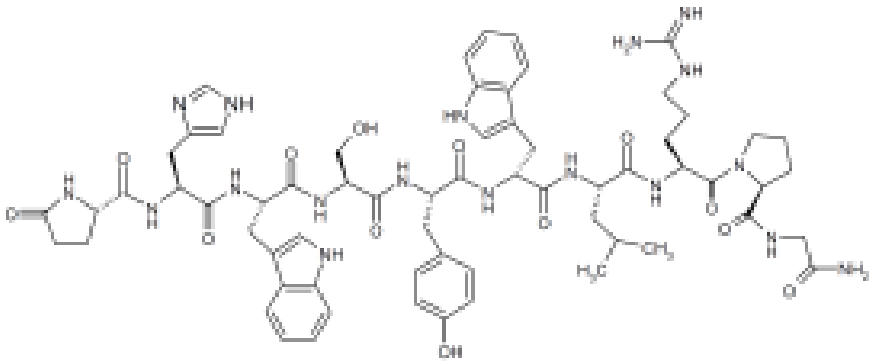
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

II.2 Drug substance

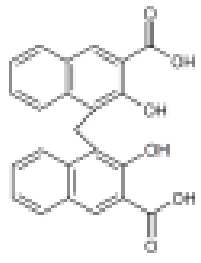
rINN: Triptorelin pamoate

Chemical name: L-pyroglutamyl-L-histidyl-L-trytophanyl-L-seryl-L-tyrosyl-D-tryptophanyl-L-leucyl-L-arginyl-L-prolyl-L-glycine-amide pamoate

Structural formula:



pGlu-His-Trp-Ser-Tyr-DTrp-Leu-Arg-Pro-Gly-NH_2 Triptorelin



Pamoic acid

Molecular formula:	$C_{64}H_{82}N_{18}O_{13}$ (triptorelin) $C_{23}H_{16}O_6$ (pamoic acid)
Relative molecular mass:	Triptorelin: 1311.46 Pamoic acid: 388.4
Appearance:	Pale yellow powder
Solubility:	In the range of solvents tested, triptorelin pamoate is insoluble in every case, except in dimethylsulphoxide, ethanol/water mixture, methanol and methanol/water mixture.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a powder and solvent for suspension for injection, containing the active substance triptorelin pamoate, with the same pharmacokinetics, pharmacodynamics, efficacy and safety as Decapeptyl SR 11.25 mg Powder for suspension for injection existing 11.25 mg acetate formulation (PL 34926/0003). Suitable product development data have been submitted with this application.

All excipients comply with their respective European Pharmacopoeia monograph, except for D, L-lactide co-glycolide polymers, which is controlled to an in-house specification.

None of the excipients are of human or animal origin, and none are sourced from genetically modified organisms.

There were no novel excipients used.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. The manufacturing process has been validated using commercial-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. In-house working standards are used, which have been compared to European Pharmacopoeia references, where available. Certificates of Analysis from commercial-scale batches have been provided that are in line with the finished product specification.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing. The results from these studies support a shelf life of 3 years for the unreconstituted (unopened) product, with the special storage condition, “Do not store above 25°C”. The product should be used immediately after reconstitution.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for this product.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance triptorelin pamoate are well-known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology, pharmacokinetics and toxicology.

Most of the non-clinical data obtained with triptorelin were generated with the acetate salt. The applicant has generated a comprehensive series of toxicity studies conducted with triptorelin as triptorelin acetate. The systemic toxicology of the pamoate and acetate formulations were compared using 6-month toxicology studies, which showed similar results. This confirms that data from one salt/formulation could be extrapolated to the other. The active circulating moiety for both salts is the free peptide triptorelin. The information concerning the toxicity of pamoic acid confirms that that there is no concern about potential toxicity of the pamoate ion. Since the active, circulating moiety for the acetate and pamoate salts formulation is the free peptide (triptorelin), further repetition of some toxicity studies already conducted with the acetate salt, was not deemed necessary with the pamoate salt.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

Since this product is intended to be used in substitution with other products that are currently marketed, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is a line-extension of Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection (PL 34926/0003), representing a change in active substance from triptorelin acetate to triptorelin pamoate. Clinical data have been submitted to show that the active substance triptorelin pamoate has the same pharmacokinetic (PK), pharmacodynamic (PD) and efficacy properties as triptorelin acetate.

IV.2 Pharmacokinetics

The applicant has submitted PK data to support this application. Bioequivalence to the approved 11.25 mg acetate formulation is not claimed. Instead, therapeutic equivalence is shown based on pharmacodynamic endpoints.

Study E-47-52014-402L

This was a 3-month, randomised, open-label study comparing the 3-month pamoate formulation with the 1-month acetate formulation in men with prostate cancer (for full description see part IV). An objective was to establish the PK profile of the 3-month pamoate formulation, including AUC_{0-84}, C_{max} and T_{max}. The PK sub-study included 12 patients. Blood samples were collected at baseline (pre-dose) and 1, 2, 4, 8, 12, 24 and 48 hours, and 7, 10, 14, 17, 21, 24, 28, 31, 35, 38, 42, 45, 49, 52, 56, 59, 63, 66, 70, 73, 77, 80, 84, 87, and 91 days post dose.

Table 1: Summary statistics for PK sub-set patients

	Cmax (ng/ml)	Tmax (h)	AUC1 (d.ng/ml)	AUC2 (d.ng/ml)	Last Day
	25.31	1.8	24.7	22.54	93
	0.85	24.0	7.30	6.10	51
	0.28	24.0	5.28	3.78	51
	28.09	1.0	19.93	-	91
	11.69	2.0	10.52	5.93	99
	29.39	4.5	22.33	18.98	91
	33.73	2.5	12.65	10.79	91
	27.97	4.5	24.59	21.61	87
	26.20	3.0	17.07	15.43	56
	26.92	5.0	22.12	21.00	56
	8.04	5.0	9.00	8.16	42
	9.02	3.0	7.73	6.89	42
Mean	22.64	3.2	19.12	15.97	
SD	9.33	1.4	6.13	7.27	
Minimum	8.04	1.0	10.52	5.93	
Maximum	33.73	5.0	24.70	22.54	
N	10	10	6	5	

Notes

AUC1 is the AUC to the last day for which data are present
AUC2 is the AUC above baseline (up to the last day)

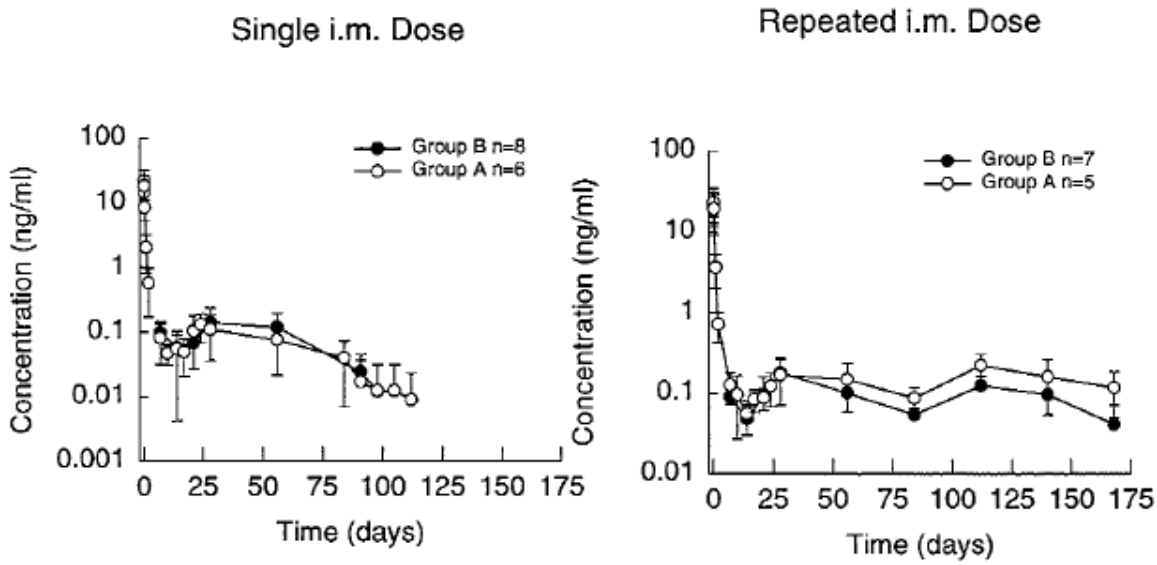
Summary statistics for AUC exclude patients who did not have data up to a least Day 70

Mean residual triptorelin levels exceeded 0.05 ng/mL at 28, 56 and 84 days. There was no accumulation of triptorelin after repeated dosing.

Study E-54-52014-099

This was a single-arm study in 29 female patients with gynaecological disorders amenable to gonadotrophin releasing hormone (GnRH) treatment. A PK sub-study was conducted. Detectable triptorelin levels were measured up to 84 days after a single injection of the 3-month pamoate formulation, with a C_{max} of 23.8 ng/mL, T_{max} of 2.4 hours and $AUC_{0\text{-}84\ days}$ of 22.29 ng /mL.day.

Figure 1: Mean PK profiles of triptorelin



Study 2-54-52014-143

This was a single-arm study in 37 paediatric patients with central precocious puberty. Plasma levels of triptorelin were measured at baseline and 1, 2, 3, 4, 5, and 6 months. Mean ± standard deviation (SD) triptorelin values were 0.034±0.02 ng/mL at 3 months and 0.030±0.02 ng/mL at 6 months, showing no accumulation after a second administration. Based on a PK/PD model, it was estimated that the triptorelin level needed to decrease luteinising hormone (LH) to ≤ 3 IU/L was 10 pg/mL. A triptorelin level of 40 pg/mL was required to ensure that 95% of patients would be controlled.

It is agreed with the applicant that the demonstration of PK equivalence between the proposed 11.25 mg pamoate formulation, and the approved 3.25 mg and 11.25 mg acetate formulations is not required.

The PK data submitted for the 3-month pamoate formulation demonstrates that triptorelin levels initially peak and then decrease to a plateau that is sustained for the 3-month dosing interval.

The pharmacokinetic characteristics of the active substance (distribution, elimination, PK in special populations, interactions) are well-known, and do not require discussion as part of this line-extension application.

IV.3 Pharmacodynamics

As an analogue of natural GnRH, triptorelin binds competitively to high affinity gonadotrophin receptors in the pituitary. This causes an initial surge in LH and follicle stimulating hormone (FSH) blood levels, consequently increasing serum testosterone levels in men and oestradiol (E2) levels in women. Prolonged exposure of pituitary gonadotrophin receptors to triptorelin leads to desensitisation. This causes LH and FSH levels to decrease to concentrations that suppress testicular and ovarian function, and results in castration levels of serum testosterone and E2. The suppression of hormone levels continues for as long as triptorelin is present at therapeutic concentrations. Treatment of hormone-dependent prostate cancer with GnRH analogues results in androgen deprivation and resultant apoptosis of prostate cancer cells. In endometriosis, the primary aim of treatment with triptorelin is a suppression of E2 production to post menopausal levels. This suppresses menses, leading to a reduction in endometriotic deposits and an improvement in clinical symptoms. In central precocious puberty, suppression of LH and FSH secretion induces gonadal suppression of ovarian or testicular hormone production and secretion.

IV.4 Clinical efficacy

The evaluation of clinical efficacy is based mainly on the outcomes of PD endpoints. The discussion of the efficacy data for each indication can be found in the relevant under the relevant heading as follows, IV.4.1 (prostate cancer), IV.4.2 (endometriosis) and IV.4.3 (precocious puberty).

No formal dose-response studies were conducted. The absence of any formal dose- response studies is acceptable since the 11.75 mg strength triptorelin acetate formulation is approved in the UK for administration every 3 months to treat the below indications.

IV.4.1 Clinical efficacy: prostate cancer

In support of this line-extension application for the 3-month (11.25 mg) pamoate formulation, the applicant has submitted data from a number of pivotal and supportive studies.

The main pivotal study in support of the 3-month pamoate formulation (when administered intramuscularly) is E- 47-52014-402(L), a randomised comparison against the 1-month acetate formulation. In addition, the applicant has conducted a 1-year, single-arm study of the 3-month pamoate formulation (Study E-54-52014-087). These studies are described below.

Study A-93-52014-071 compared the efficacy of the 3-month pamoate formulation and the 1-month acetate formulation over 2 years after a run-in of the 1-month formulation for 3 months. E 47-52014-402 compared the efficacy of the 3-month pamoate formulation and the 1-month acetate formulation over 3 months. E-47-52014-401 was an extension study to E-47-52014-402 and provided long-term efficacy data. An additional two studies of the 3-month pamoate formulation in prostate cancer have been submitted (E-47-52014-407 and E-54-52014-077). However, only 12 and 14 subjects were enrolled respectively. Therefore, these studies do not contribute significantly to the assessment of efficacy and will not be discussed further.

<u>Study E-47-52014-402(L)</u>

This was a Phase II, randomised, open-label study comparing the PK, efficacy and safety of two different sustained-release formulations of triptorelin in patients with prostate cancer. The primary objective was to compare the extent of testosterone suppression to castrate levels over 3 months. Testosterone castration level was defined as 3nmol/l. However, results were also analysed using the definition of 1.73 nmol/l. The study completed in 1996.

Eligible patients had histologically proven prostate cancer, due to be treated by androgen deprivation, to which they were naïve. Serum testosterone was required to be in the normal range (8.5 – 30 nmol/l). Patients at serious risk of complications in case of tumour flare, e.g. vertebral metastases threatening spinal cord compression or significant obstructive uropathy, were excluded. The study population is not

representative of all the prostate cancer populations for which the proposed product is intended. However, in this case the results can be extrapolated to other prostate cancer populations for whom medical castration is indicated because the demonstration of comparable testosterone suppression is likely to be independent of disease stage.

Patients were randomised 2:1 to receive either a single intramuscular injection of the 3-month formulation (11.25mg triptorelin pamoate) or three 1-monthly intramuscular injections of the 1-month formulation (3.75mg triptorelin acetate).

The primary endpoint was the proportion with castrate serum testosterone level at 84 days. Testosterone, FSH, LH and prostate specific antigen (PSA) were assayed by commercially available kits using validated radioimmunoassay (RIA). Blood samples were collected at baseline (pre-dose), 1, 2, 7, 14, 21, 28, 42, 56, 70, 77, 84 and 91 days.

According to Appendix 4 to the *Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA/CHMP/703715/2012 Rev. 1)*, for products aiming at achieving medical castration it is sufficient to convincingly demonstrate the achievement and maintenance of castration levels of testosterone in the absence of breakthroughs and micro-surges.
Data are presented below for the efficacy evaluable population. An intention-to-treat (ITT) population is preferred. However, any exclusions due to low pre-treatment testosterone affected each treatment group equally, and are therefore unlikely to affect the study conclusions.

Table 2: Summary of serum testosterone (nmol/l) at each time point: efficacy evaluable population

Treatment	Statistics	Baseline	Day 0	Day 1	Day 2	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	Day 70	Day 77	Day 84	Day 91
Acetate:															
	Mean	15.85	14.18	22.06	22.16	18.41	5.79	1.57	0.89	0.82	0.80	0.85	0.80	0.80	0.84
	SD	4.40	5.04	8.70	6.84	10.21	3.09	1.03	0.23	0.07	0.00	0.19	0.00	0.00	0.13
	Minimum	9.10	9.40	12.90	10.20	8.90	1.90	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80
	Median	15.40	12.50	20.60	20.70	16.45	4.90	1.40	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80
	Maximum	26.30	31.30	51.70	34.80	57.70	12.90	5.10	1.70	1.10	0.80	1.60	<0.80	0.80	1.30
	N	21	21	21	20	20	20	18	20	17	19	17	13	18	14
No. patients (%) below castrate level:															
	3 nmol/L	0	0	0	0	0	2 (10%)	17 (94%)	20 (100%)	17 (100%)	19 (100%)	17 (100%)	13 (100%)	18 (100%)	14 (100%)
	1.73 nmol/L	0	0	0	0	0	0	13 (72.2%)	20 (100%)	17 (100%)	19 (100%)	17 (100%)	13 (100%)	18 (100%)	18 (100%)
Pamoate:															
	Mean	17.12	16.11	24.46	27.19	21.01	5.55	1.73	0.87	0.83	0.82	0.82	0.83	0.82	0.87
	SD	5.61	5.26	12.91	11.96	9.29	2.48	1.01	0.21	0.11	0.10	0.09	0.12	0.06	0.24
	Minimum	9.00	6.70	10.40	8.10	7.50	1.20	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80
	Median	16.30	16.70	22.70	24.35	18.80	5.10	1.60	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80
	Maximum	36.00	29.70	92.50	70.50	49.80	11.00	6.30	2.00	1.30	1.40	1.25	1.50	1.10	2.10
	N	49	48	48	48	48	43	49	49	46	48	42	42	45	37
No. patients (%) below castrate level:															
	3 nmol/L	0	0	0	0	0	8 (19%)	45 (92%)	49 (100%)	46 (100%)	48 (100%)	42 (100%)	42 (100%)	45 (100%)	37 (100%)
	1.73 nmol/L	0	0	0	0	0	1 (2.3%)	28 (57.1%)	48 (98.0%)	46 (100%)	48 (100%)	42 (100%)	42 (100%)	45 (100%)	37 (100%)

At 28 days, all subjects had achieved castration levels except one subject in the pamoate group (2.0%). All subjects included in the efficacy evaluable population attained castration serum testosterone (1.73 nmol/l) by 84 days.

The numbers efficacy evaluable patients are reduced over time in both groups. If subjects not providing data at 84 days are assumed to have failed treatment, then the proportions considered castrated (≤1.73 nmol/l) are 91.8% for the 3-month pamoate group compared to 85.7% for the 1-month acetate group. Based on this worst-case scenario, the triptorelin pamoate formulation has comparable efficacy to the triptorelin acetate formulation, in terms of testosterone suppression.

Mean time to castration (1.73nmol/l) was 20.4 days (SD = 3.2) for the triptorelin pamoate group compared to 20.3 days (SD 2.8) for the triptorelin acetate group. Mean FSH and LH levels increased to peak levels at 1 day, and then reduced to levels below baseline for the remainder of the study. Mean levels were comparable between treatment arms at all timepoints. At 84 days, mean FSH was 4.09 IU/L for the triptorelin pamoate group compared to 4.32 IU/L for the triptorelin acetate group. At 84 days, mean LH was 0.60 IU/L in both groups. PSA levels fell to < 4.0 ng/mL by 84 days in 34 out of 48 (70.8%) providing data in the triptorelin pamoate group, compared to 14 out 19 (73.6%) subjects providing data in the triptorelin acetate group.

Study E-54-52014-087

This was a 1-year, open-label, uncontrolled safety study of 3-monthly triptorelin pamoate in patients with prostate cancer requiring hormone therapy. The primary objective was to investigate the long-term safety and efficacy of prolonged-release triptorelin pamoate 11.25 mg, administered intramuscularly every 3 months. The study completed in 1997.

Eligible patients had prostate adenocarcinoma with lymph node involvement or distant metastases, had not been treated for metastatic disease, and required androgen deprivation. Serum testosterone had to be ≥ 1ng/mL and ECOG ≤ 2 at screening.

Triptorelin pamoate 11.25 mg was administered intramuscularly every 3 months for 1 year. Flutamide 250 mg was administered orally three-times daily from baseline to 28 days to reduce the risk of tumour flare.
Although primarily a safety study, efficacy assessments included measuring testosterone, LH, FSH and PSA levels. Sampling was conducted at 1, 2, 3, 6, 9 and 12 months. The main efficacy endpoint was % subjects achieving castration at each timepoint. Castration was defined as serum testosterone ≤0.5 ng/mL (≤1.73 nmol/L).

The efficacy analyses were based on the ITT population, i.e. all 86 patients that were dosed.

Table 3: Summary of serum testosterone

Testosterone level (nmol/L)	Day -7 n (%)	Month 1 n (%)	Month 6 n (%)	Month 12 n (%)	Last value in study n (%)
N	86	84	75	63	86
<0.3467	0	11 (13.3)	7 (9.6)	2 (3.3)	4 (4.8)
0.3467 to 1.0401	0	58 (69.9)	47 (64.4)	29 (47.5)	42 (50.6)
1.0401 to 1.7335	0	12 (14.5)	12 (16.4)	24 (39.3)	29 (34.9)
>1.7335 (i.e. not castrated)	85 (100)	2 (2.4)	7 (9.6)	6 (9.8)	8 (9.6)

n = number of patients in category; N = number of patients at visit.

Of the evaluable patients at 6 months, 90.4% had testosterone suppression to castration levels at 6 months. At 12 months, the proportion achieving castration was similar (90.2%).

The numbers evaluable for efficacy are reduced over time. If patients not providing data at 6 months and 12 months are assumed to have failed treatment, then the proportions achieving castration (≤1.73 nmol/l) are 79.1% and 66.3%, respectively.

Tumour size, according to the European Organisation for Research and Treatment of Cancer(EORTC) criteria was assessed in 63 patients at 12 months. Fifteen patients (23.8%) had a complete response, 15 patients (23.8%) had a partial response and 10 patients (15.9%) had stable disease. PSA, FSH and LH concentrations decreased during the study, based on the comparison of mean values for last observation compared to screening visit.

Study A-93-52014-071

This was a randomised, open-label study comparing the PK, PD and safety of the 3-month triptorelin

pamoate formulation versus to the 1-month triptorelin acetate formulation.

Male patients with locally advanced or metastatic prostate cancer, a World Health Organisation (WHO) performance status 0-2, and a life expectancy of more than 6 months were eligible. All subjects received the 1-month triptorelin acetate formulation for a 3-month run-in period. Subjects were then randomised to either triptorelin pamoate 11.25 mg administered intramuscularly every 3 months for 2 years or triptorelin acetate 3.75 mg administered intramuscularly monthly for 2 years.

A total of 77 patients were randomised, 40 to the 3-month pamoate group and 37 to the 1-month acetate group. Of the 77 randomised patients, 41 completed the study - 19 in the 3-month triptorelin pamoate group and 22 in the 1-month triptorelin acetate group. After 3 months of treatment, mean testosterone levels were 0.26 ng/mL (with a standard error [SE] = 0.19) for the 3-month triptorelin pamoate group compared to 0.44 ng/mL (SE = 0.02) for the 1-month triptorelin acetate group. At 24 months, mean levels were 0.24 (0.019) ng/mL for the 3-month triptorelin pamoate groupand 0.26 (0.025) ng/mL for the 1-month triptorelin acetate group.

The proportion of patients maintaining castration levels of testosterone was not reported. However, the mean values were comparable. These data support the comparable efficacy of the 3-month triptorelin pamoate and 1-month triptorelin acetate formulations.

Study E-47-52014-402

This was a randomised, open-label study investigating the PK of two sustained-release formulations of triptorelin in patients with prostate cancer, including an 11.25 mg triptorelin pamoate formulation.

Patients had histologically confirmed prostate cancer for which androgen deprivation was indicated, but who had not yet received androgen deprivation therapy. Eligible patients were randomised 2:1 to receive treatment with a single intramuscular injection of the 11.25 mg triptorelin pamoate formulation or an intramuscular injection of the 3 mg triptorelin acetate formulation every 4 weeks for 3 months. Key efficacy endpoints included serum testosterone levels at 84 days (mean value and percentage responders), time to reach castration level and mean FSH/LH. Blood samples were collected at 0, 1, 2, 7, 14, 21, 28, 42, 56, 70, 77, 84 and 91 days. Castration levels of testosterone were defined as ≤ 1.73 nmol/L.

A total of 63 patients received study drug, 41 received the triptorelin pamoate formulation and 22 received the triptorelin acetate formulation. Two patients from each group were excluded from the efficacy evaluation due to low testosterone levels at baseline. An additional patient withdrew from the pamoate arm after 2 days and was excluded from the efficacy analysis. The mean time to reach castrate levels was 19.5 days for the triptorelin acetate group compared to 18.7 days for the triptorelin pamoate group. 100% of evaluable patients were within the castrate range at 28 days and 84 days. By 28 days, 100% of patients were castrated (for the less strict target of ≤ 3.0 nml/L). FSH and LH values rose initially, and then fell to below treatment values for the remainder of the study. PSA levels reduced to within the normal range (< 4 ng/ml) by 84 days for 74.4% of those in the triptorelin pamoate group, compared to 72.7% of those in the triptorelin acetate group.

It is not known how many patients were randomised but did not receive study drug. However, it is known that two patients in the acetate arm and three patients in the pamoate arm were excluded from the efficacy evaluation. If it assumed that these patients did not have testosterone below castration levels at 84 days, then the proportion castrated at 84 days is reduced to 92.7% and 90.9% for triptorelin pamoate and triptorelin acetate groups, respectively. This study provides additional evidence of comparative efficacy.

Study E-47-52014-401

This study was an open-label extension of Study E-47-52014-402. The main objective was to assess long-term efficacy, in maintaining testosterone within castration levels. The study enrolled 49 patients

who completed Study E-47-52014-402 with testosterone at castration level (≤ 1.4 nmol/L). Subjects received a further three doses of triptorelin pamoate 11.25 mg at 3-monthly intervals by intramuscular injection.

Forty-four subjects provided data on testosterone levels. At the 3 months, 6 months and 9 month, testosterone was within castration levels (<1.73 nmol/L) for 100% of evaluable subjects.

This study provides evidence of long-term efficacy, as measured by the maintenance of testosterone within castration levels.

Overall conclusions on clinical efficacy in prostate cancer

Evidence of efficacy in prostate cancer comes from two pivotal and three supportive studies. Two studies compare the 3-month triptorelin pamoate formulation with the 1-month triptorelin acetate formulation. The studies included patients with locally advanced and metastatic disease, which is appropriate. The primary endpoint of percentage patients with testosterone suppression to castration levels is an accepted surrogate clinical endpoint for benefit of GnRH analogues in prostate cancer. The treatment duration of up to 1 year was adequate to characterise the longer-term efficacy of 3-monthly injections.

When evaluable patients are considered, testosterone suppression to castration levels is achieved in well over 90% of subjects from the 28-day timepoint onwards. In a conservative analysis where unevaluable or withdrawn subjects were considered treatment failures, the percentage castraione decreased, as expected, but remained comparable between the 1-month triptorelin acetate and 3-month triptorelin pamoate groups. Outcomes for secondary efficacy endpoints, such as FSH, LH and PSA, were also comparable between formulations.

In conclusion, efficacy has been demonstrated for the 3-month triptorelin pamoate formulation for the treatment of prostate cancer.

IV.4.2 Clinical efficacy: endometriosis

In support of this line-extension application for the 3-month (11.25 mg) triptorelin pamoate formulation, the applicant has submitted data from a number of pivotal and supportive studies. The most relevant study for this line-extension application is Study E-54-52014-099, an open-label, single-arm study of the 3-month triptorelin pamoate formulation.

Study E-54-52014-099

This was a parallel-group, multicentre study comparing a single intramuscular injection of 11.25 mg prolonged-release triptorelin pamoate versus two intramuscular injections of 11.25mg prolonged-release triptorelin pamoate. The objective was to establish the efficacy of the 3-month triptorelin pamoate formulation by measuring time to reach castration (E2 levels below 184 pmol/L [50 pg/ml]) and the duration of castration.

The study completed in 1998.

All female patients were aged 18 to 43 years, with a gynaecological condition capable of improvement by cessation of menstruation (e.g. endometriosis or fibroids), regular menstruation (cycle length 21 to 35 days) and normal ovarian function (as measured by FSH, LH and E2).

Patients received either a single intramuscular injection of prolonged-release triptorelin pamoate 11.25 mg or two intramuscular injections of prolonged-release triptorelin pamoate 11.25 mg, given 3 months apart. Blood samples were taken for oestradiol (E2) analysis ay baseline (pre-dose) and at 7, 14, 21, 28, 56, 84, 91, 98, 105, 112, 140 and 168 days. Patients receiving the two intramuscular injections had additional samples taken at 196, 224, 252, 280, 308 and 336 days.

The primary endpoints were:

- T_{lag} (time to reach castration): time in days between the injection and E2 levels reaching <184 pmol/L (50 pg/ml)

- T_{cast} (duration of castration): time in days during which E2 levels remained below the castration level.

T_{lag} and T_{cast} were also calculated using the stricter definition of castration, i.e. E2 levels reaching <110 pmol/L (30 pg/ml).

Secondary endpoints included FSH/LH and time to return to menses.

The proportion of patients attaining E2 below the castration level at 84 days would have been the preferred primary endpoint.

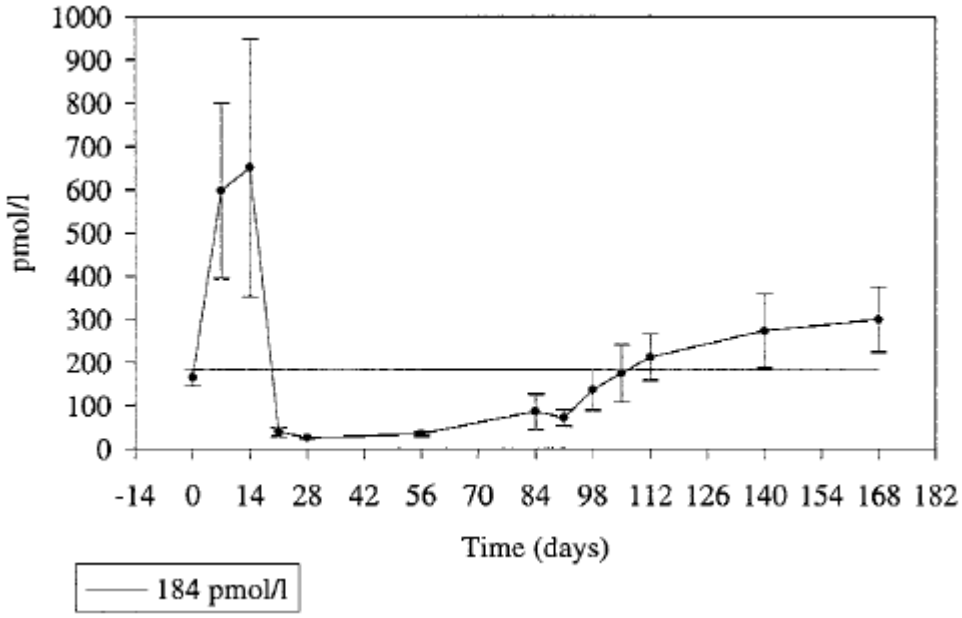
A justification for the castration level of E2 has not been provided. However, a satisfactory justification for a target E2 level of 30-50 pg/mL was provided by the applicant in a previous application for the 3-month triptorelin acetate formulation.

Single-dose group

Table 4: Single-dose injection: Time to reach castration (T_{lag}) and duration of castration (T_{cast})

Castrate level	Variable (days)	n	Median	Mean	SD	SEM	min	max	Conf. Int. 95 % lower	upper
184	Tlag	14	11.0	12.3	6.69	1.79	2.1	20.8	8.8	15.8
	Tcast	13	98.1	98.0	23.90	6.63	54.8	135.7	85.0	111.0
110	Tlag	14	12.3	13.5	7.05	1.88	2.1	23.3	9.8	17.2
	Tcast	14	91.4	87.1	23.25	6.21	45.9	126.5	74.9	99.2

Figure 2: Single-dose injection: Mean E2 levels



All patients were castrated (<110 pmol/L) before 84 days (the maximum time to reach castration was 23 days). However, at 84 days one patient had E2 levels above 184 pmol/L. Therefore, the percentage castrated at 84 days (the preferred primary endpoint) was 92.9%. The initial increase in mean E2 levels corresponds to the initial FSH/LH surge which is a characteristic of GnRH analogue treatment.

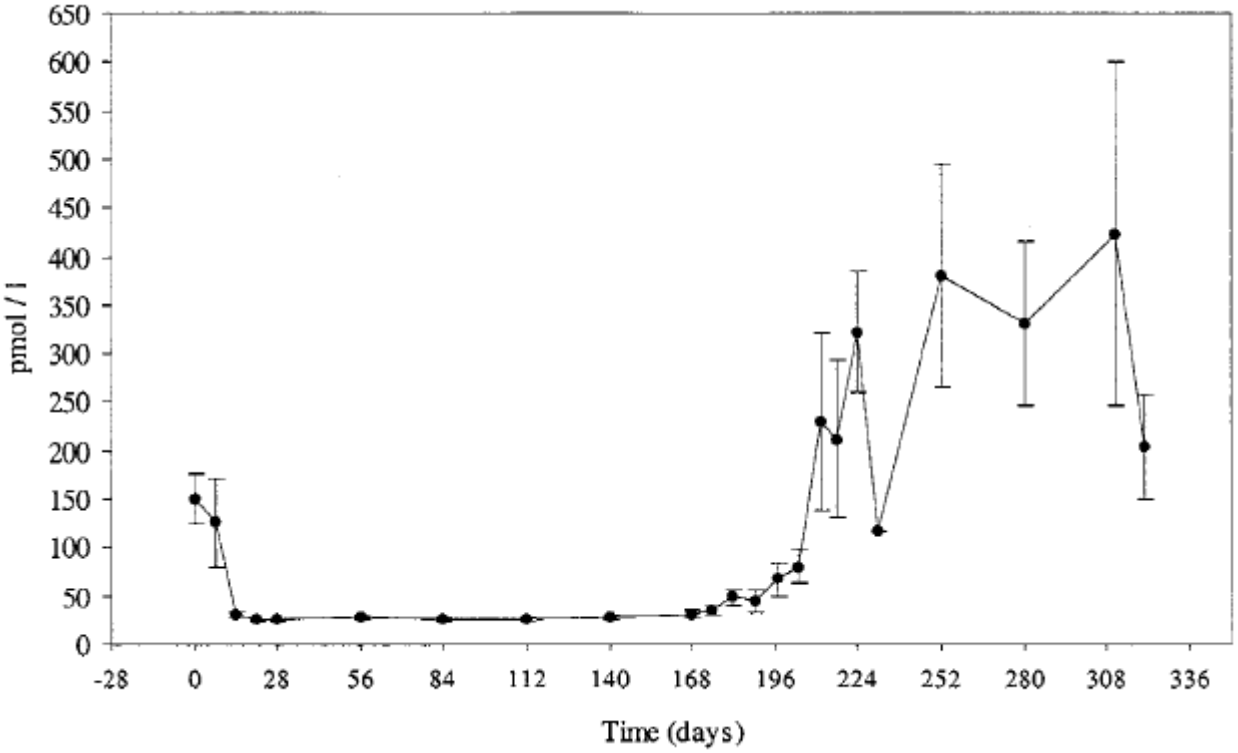
The mean time to exit from castration (<110 pmol/L) was 100.5 days (SD = 19.7). The mean time to return to menses was 134.2 days (SD = 19.5).

Two-dose group

Table 5: Two-dose injections: time to reach castration (T_{lag}) and duration of castration (T_{cast})

Variable (days)	Castrate level	n	Median	Mean	SD	SEM	min	max	Conf. Int. 95 % lower	upper
Tlag	184	12	7.0	9.6	3.81	1.10	6.0	16.4	7.1	12.0
	110	12	8.4	10.2	4.06	1.17	6.0	18.5	7.6	12.7
Tcast	184	10	201.5	205.5	15.74	4.98	183.0	242.1	194.2	216.7
	110	10	197.8	197.4	16.61	5.25	167.5	223.4	185.5	209.3

Figure 3: Group 2 injections: E2 levels (mean ±SEM)



All patients were castrated before 84 days (the maximum time to reach castration was 18.5 days). The minimum duration of castration was 167.5 days. Therefore, all patients were castrated (<110 pmol/l) at 84 days and sustained castration until at least 84 days after the second injection.

The mean time to exit from castration (<110 pmol/L) was 207 days (SD = 14.5). The mean time to return to menses following the second injection was 151.5 days (SD = 16.0).

If the results for both groups are pooled, the mean time to reach castration (E2 < 110 pmol/l) after the first injection was 12.0 days (SD = 6.0) and the overall percentage castrates (E2 < 110 pmol/l) at 84 days was 96.2%. The lower bound of the 95% confidence interval (CI) for this estimate is 88.9%.

Overall conclusions on clinical efficacy in endometriosis

For context, the results of Study E-54-52014-099 should be compared to those of Study E28-52014-705, the pivotal study supporting the approval of the 3-month triptorelin acetate formulation in the UK.

Study E28-52014-705was a randomised, open-label, parallel-group multi-centre study in 152 patients with endometriosis. Of these, 75 women were randomised to receive the test formulation (Decapeptyl SR 3-month) and 77 to receive the reference formulation (Decapeptyl 28-day) for 3 months. The definition of E2 castration was identical between the studies. 94% of patients in the 3-month group and

91% in the 28-day group reached the pre-defined castrate E2 level at 84 days (ITT). The respective pooled proportion of over 96% for the triptorelin pamoate study (Study E-54-52014-099) is in-line with this, although the numbers are smaller and, therefore, the precision reduced. In the triptorelin acetate study (Study E28-52014-705), the mean time to castration (E2<110 pmol/l) for the 28-day formulation was 11.1 days, which is similar to the 12.0 days observed for the triptorelin pamoate study (Study E-54-52014-099). In the triptorelin acetate study (Study E28-52014-705), the mean duration of castration was 85.5 days after three doses of the 1-month triptorelin acetate formulation compared to 87.1 days after a single dose of the 3-month triptorelin pamoate formulation (Study E-54-52014-099).

The data to support the efficacy of the 3-month triptorelin pamoate formulation in the treatment of endometriosis come from a relatively small, single-arm study. However, the outcomes are in-line with those expected based on the data submitted in support of the 3-month triptorelin acetate formulation. In conclusion, the clinical efficacy data to support the endometriosis indication is adequate.

IV.4.3 Clinical efficacy: precocious puberty

Central precocious puberty (CPP) refers to the development of gonadotrophin dependent onset of puberty before 8 years for girls and 9 years for boys. Precocious puberty is caused by early secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH), which induce early secretion of gonadal hormones by the ovaries or testes. As a consequence, pubic and axillary hair grow and the child's body shape and behaviour change. Acne may also appear. Boys develop facial hair and their penis lengthens. Girls develop breasts and may have menstrual periods. Growth velocity accelerates, initially inducing a rapid height increase, but this stops at an early age. Accelerated bone maturation leads to shorter final heights than would otherwise be expected. The purpose of the triptorelin therapy in this indication is to induce gonadal suppression of ovarian or testicular hormone production and secretion. This in turn leads to arrest or regression of pubertal development and also causes a reduction in the velocity of bone maturation.

The following precocious puberty indication is approved for the 11.25 mg triptorelin acetate formulation, and is proposed for the 11.25 mg triptorelin pamoate formulation:

- Treatment of precocious puberty (onset before 8 years in girls and 10 years in boys).

The most relevant study for this line extension application is Study 2-54-52014-143, a multicentre, single-arm, open-label study of the 3-month triptorelin pamoate formulation for the treatment of CPP. The ongoing extension study, Study 2-54- 52014-159, is a long-term follow-up of Study 2-54-52014-143. Data from this study are not yet available.

<u>Study 2-54-52014-143</u>

This was a multicentre, non-comparative, open-label study to assess the efficacy of triptorelin pamoate 11.25 mg with respect to the proportion of patients with suppressed LH response (LH ≤ 3 IU/L) following two injections of triptorelin pamoate 11.25 mg administered intramuscularly at intervals of 3 months . The primary objective was to assess the proportion of patients with suppressed LH response (LH ≤ 3 IU/L) to a GnRH test performed 3 months after injection with triptorelin 11.25 mg.
To be eligible, patients had CPP (defined as the onset of sexual characteristics development [Tanner method, had a pubertal response of LH to a GnRH test (LH ≥ 5 IU/L), and a difference in bone age (chronological age >1 year and testosterone level ≥ 0.5 ng/mL [inboys]). The eligibility criteria define an appropriate CPP population
Patients received a total of two intramuscular injections of triptorelin pamoate 11.25 mg, 3 months apart. Treatment was then continued until aged 11 (girls) or 13 (boys) as part of a follow-up study (Study 2-54-52014-159).
The primary efficacy endpoint was the proportion of patients with a maximum peak LH ≤ 3 IU/L in response to GnRH at 3 months. The GnRH test was performed while stimulating the gonadotrope axis with 100 µg/m^2 IV of GnRH. FSH response to GnRH test at 3 and 6 months, and LH response to GnRH test at 6 months were also measured. Oestradiol (girls) and testosterone (boys) was measured monthly to assess the proportion of patients in the pre-pubertal range (oestradiol ≤ 20 pg/mL; testosterone ≤0.3

ng/mL). Other endpoints included pubertal stage and growth velocity at months 3 and 6, and the difference between bone age and chronological age at month 6.

The primary endpoint was the same as Study E8-52014-708, conducted with the 3-month triptorelin acetate formulation, which supported the approval of the precocious puberty indication for a previous application.

Only one male subject was enrolled in the study, reflecting the fact that CPP is 10 times more common in girls. The primary analysis was performed on the ITT population. In addition, a modified ITT (MITT) analysis excluded data from two patients who were withdrawn from the study due to being overweight (violation of eligibility criteria by two patients) and who did not provide complete efficacy data at 3 months due to vomiting (one patient). Results for the Per-Protocol (PP) population are also presented below.

Table 7: Proportion of patients with GnRH-stimulated peak LH ≤ 3 IU/L at 3 months

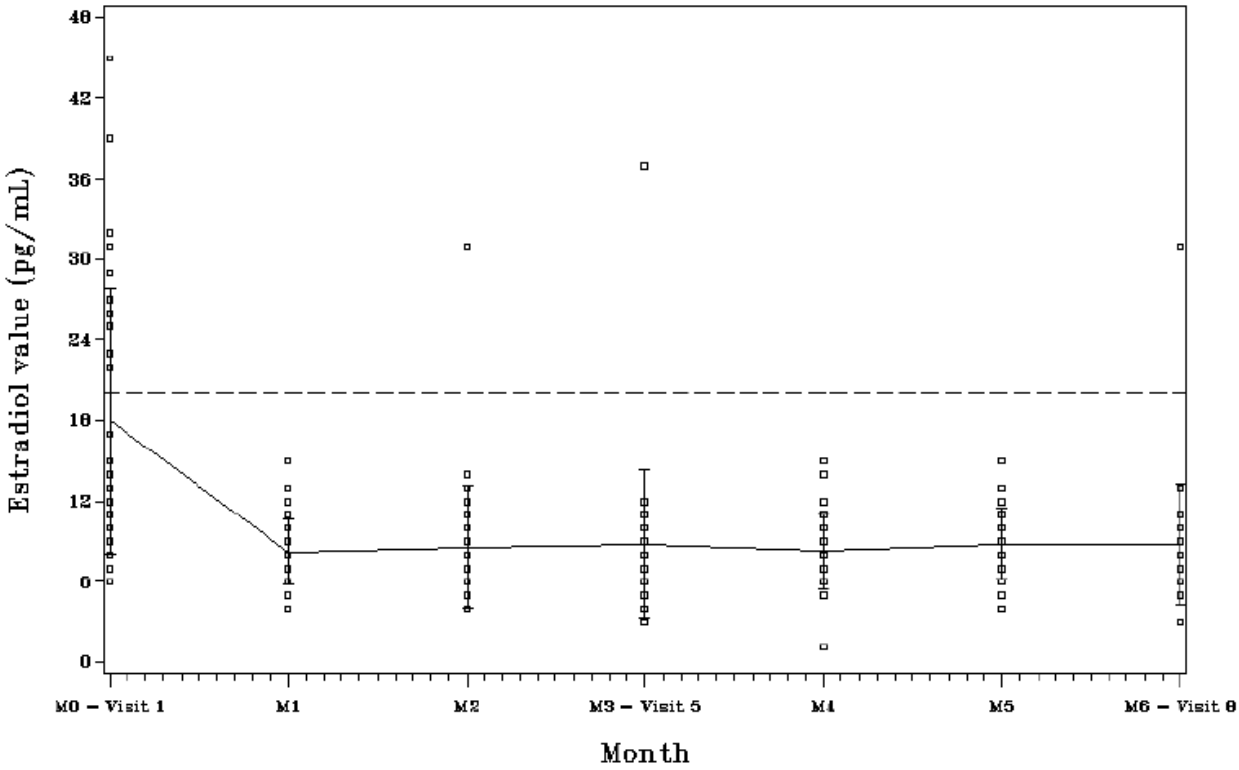
Population Responder status	All Patients Number (%) Patients	95% CI[a] Number (%) Patients	p-Value[b] (One-sided)
ITT (N=37) Primary efficacy analysis (worst case scenario)			
Yes	31 (83.8%)	(68.0% to 93.8%)	0.0440
No	6 (16.2%)	-	-
ITT (N=37) Sensitivity analysis (replacing missing T15 evaluation for LH/GnRH test in one patient)			
Yes	32 (86.5%)	(71.2% to 95.5%)	0.0172*
No	5 (13.5%)	-	-
MITT (N=34)			
Yes	31 (91.2 %)	(76.3% to 98.1%)	0.0032
No	3 (8.8 %)	-	-
PP (N=32)			
Yes	30 (93.8 %)	(79.2% to 99.2%)	0.0012
No	2 (6.3 %)	-	-

It is noted that if the two overweight patients are excluded, then the proportion with GnRH-stimulated peak LH ≤ 3 IU/L at 3 months is 31 out of 35 (88.6%). The proportion with GnRH-stimulated peak LH ≤ 3 IU/L at 6 months was 32 out of 37 patients (86.5%). The mean (SD) GnRH-stimulated peak FSH at 3 and 6 months were 2.32 IU/L (2.52) and 2.38 IU/L (1.66) respectively.

Testosterone levels in the only male patient enrolled were 2.0 ng/mL at baseline and were suppressed to < 0.3 ng/mL at all subsequent on-treatment visits. Genital development in the only male patient was Tanner Stage 3 at baseline and Tanner Stage 2 at 6 months.

Oestradiol levels in the female patients enrolled are shown in the following figure:

Figure 4: Individual and mean ± SD oestradiol (pg/mL) levels at each visit



At baseline, 18/36 (50%) female patients had a serum inhibin B level ≥6 pg/mL. This proportion decreased following initiation of triptorelin treatment to 1/34 (2.9%) patients at 3 months and 2/34 (5.9%) patients at 6 months. Tanner pubic hair stage and breast stage was stabilised or reduced in 30/35 (85.7%) patients and 32/34 (94.1%) patients, respectively, at 6 months. No vaginal bleeding was reported during the study.

At 6 months, there was a mean decrease on the difference between bone age and chronological age of 0.16 years (SD = 0.54).

The outcomes for the secondary biochemical and clinical endpoints are supportive of the primary analysis.

Overall conclusions on clinical efficacy: precocious puberty

The design of Study 2-54-52014-143 with the 3-month triptorelin pamoate formulation was similar to Study E8-52014-708 with the 3-month triptorelin acetate formulation, submitted in support of a previous application. In Study E8-52014-708, 54 girls and 10 boys were included in the ITT analysis. At 3 months, 83.0% of children showed a suppressed LH response to GnRH. The corresponding proportion for Study 2-54-52014-143 was 83.6%.

Overall, it is concluded that triptorelin pamoate 11.25 mg every 3 months provided an adequate level of GnRH-stimulated LH suppression.

Based on the data submitted, the efficacy of the 3-month triptorelin pamoate formulation is expected to be comparable to the approved 3-month triptorelin acetate formulation, for the treatment of central precocious puberty.

IV.5 Clinical Safety

The safety profile of triptorelin is well-established.

In 2009, a European periodic safety update report (PSUR) work-sharing procedure was initiated for all triptorelin-containing products. As a result, an EU core safety profile identical for all triptorelin 1-month and 3-month formulations was agreed between member states. The EU agreement regarding the core safety profile suggests that the clinical safety of the 3-month pamoate formulation is comparable to that of the 1-month and 3-month acetate formulations.

Safety data collected from patients who participated in the above clinical trials showed that there was a similar safety profile between this product and other related products containing triptorelin acetate.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection.

A summary of safety concerns, as approved in the RMP, is listed below:

Summary table of safety concerns:

Summary of Safety Concerns

Endometriosis	
Important identified risks:	• loss in bone density.
Important potential risks:	• mood changes including depression. • teratogenic effects.
Missing information:	• use in pregnancy and lactation.
Uterine fibromyoma	
Important identified risks:	• loss in bone density.
Important potential risks:	• mood changes including depression. • teratogenic effects.
Missing information:	• use in pregnancy and lactation.
Female infertility	
Important identified risks:	• ovarian hyperstimulation syndrome.
Important potential risks:	• mood changes including depression. • teratogenic effects.
Missing information:	• use in pregnancy and lactation.
Prostate cancer	
Important identified risks:	• tumour flare (including increased pain). • loss in bone density (osteoporosis).
Important potential risks:	• urethral obstruction. • metabolic changes (e.g. glucose intolerance). • cardiovascular disease . • mood changes including depression. • cerebral ischaemia and central nervous system haemorrhage.
Central precocious puberty	
Important potential risks:	• loss in bone density. • slipped femoral epiphysis following withdrawal of GnRH treatment. • abnormal weight gain. • teratogenic effects.
Missing information:	• use in pregnancy and lactation.
Endocrine responsive early stage breast cancer in women who are confirmed as premenopausal	
Important identified risks for the use of triptorelin in combination with tamoxifen or an aromatase inhibitor:	• osteoporosis and fractures. • hypertension. • hyperglycaemia/diabetes. • depression (including severe depression) . • thromboembolic events. • cerebral ischaemia and central nervous system haemorrhage. • cardiovascular disease.
Important potential risks:	• ovarian hyperstimulation syndrome. • teratogenic effects.
Missing information:	• use in pregnancy and lactation.
All indications	
Important identified risks:	• pituitary apoplexy. • QT prolongation. • hypersensitivity.
Important potential risk:	• medication error (incorrect route of administration).
Missing information:	• use in patients with hepatic impairment. • use in patients with renal impairment.

GnRH=gonadotropin releasing hormone.

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects

The efficacy of the 3-month triptorelin pamoate formulation for the proposed prostate cancer indications was supported by data from several single-arm and comparative studies. For the endometriosis and CPP indications, the data came from a single-arm study in each case. Although the pivotal endometriosis study was small, the precision of the estimate was acceptable given the observed treatment response. The studies were of adequate design. The populations studied were representative of the target populations. In all cases the primary efficacy endpoints were surrogate biochemical endpoints; these have been accepted previously for GnRH studies in these settings. The chosen primary endpoints facilitated comparison across studies, therefore, single-arm studies can be accepted as pivotal.

The observed extent of suppression of testosterone, E2 or LH response to GnRH, as measured by the proportion achieving a pre-defined target, was in line with that observed for 1-month and 3-month acetate formulations. Outcomes for secondary biochemical and clinical endpoints were supportive of efficacy.

No new or unexpected safety issues were observed during the trials.

The submitted clinical efficacy and safety data are adequate. The benefit/risk of the pamoate formulation of Decapeptyl SR 11.25 mg, powder for suspension for injection is considered to be comparable to the currently approved 3-month acetate formulation.

In conclusion, the benefit/risk is positive. Decapeptyl SR 11.25 mg, powder for suspension for injection is approvable. It is recommended that a Marketing Authorisation is granted for Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection.

V. USER CONSULTATION

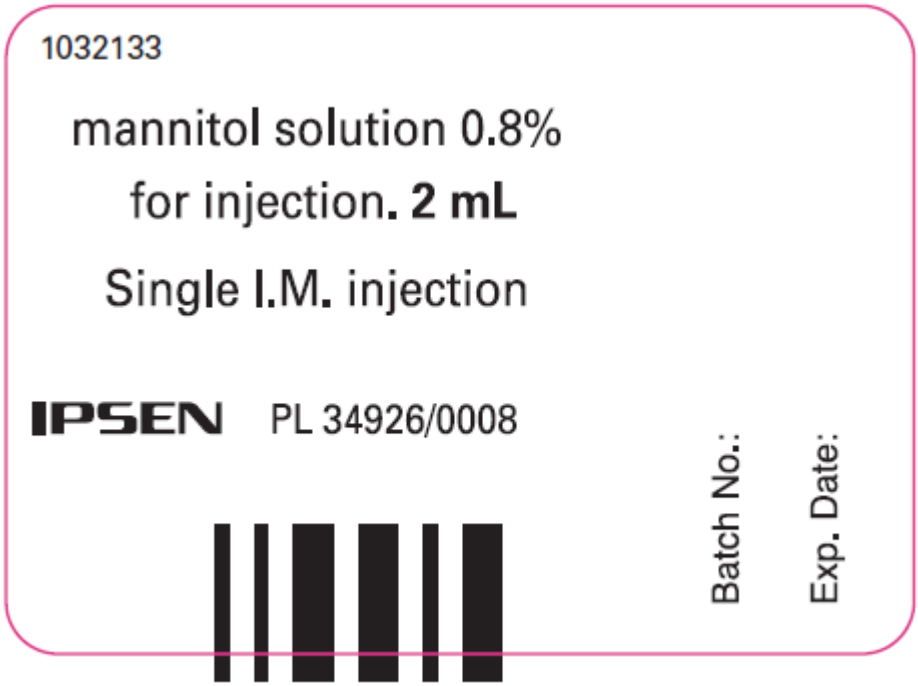
The applicant makes reference to a user consultation with target patient groups on the essentially identical Patient Information Leaflet (PIL) for Decapeptyl 11.25 mg Powder for Suspension for Injection (PL 34926/0003). This is acceptable.

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for the product granted Marketing Authorisation at a national level, are available on the MHRA website.

The approved labelling for Decapeptyl SR 11.25 mg, powder and solvent for suspension for injection is presented below:


1032133
mannitol solution 0.8%
for injection. 2 mL
Single I.M. injection
IPSEN
PL 34926/0008
Batch No.:
Exp. Date:

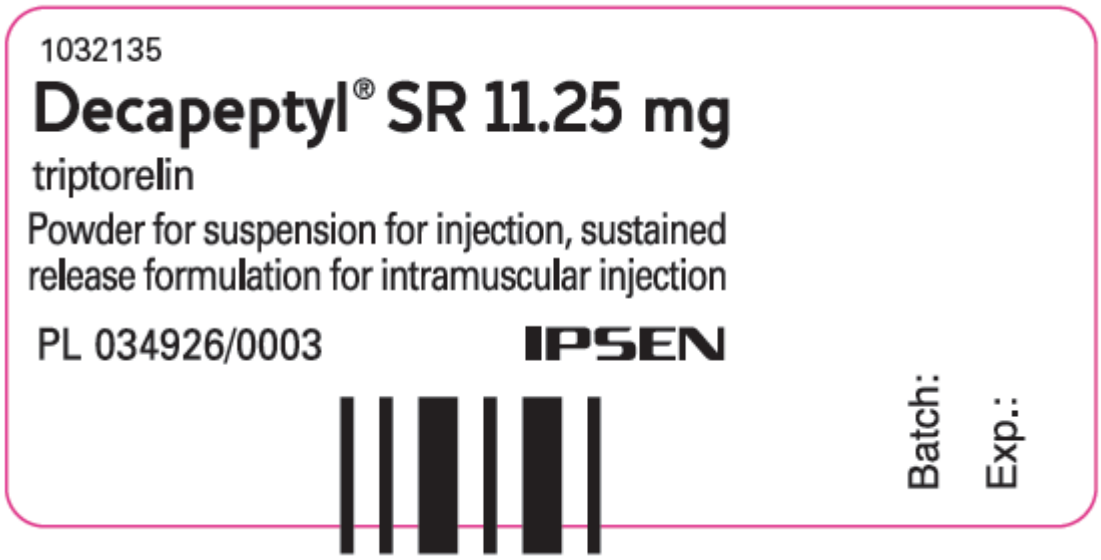

1032135
Decapeptyl® SR 11.25 mg
triptorelin
Powder for suspension for injection, sustained release formulation for intramuscular injection
PL 034926/0003
IPSEN
Batch:
Exp.:

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)