Study Protocol

A Phase II, Open-Label, Single-Arm Study to Assess the Efficacy and Safety of Decapeptyl® SR (3 mg and 11.25 mg formulations) when administered by subcutaneous injection.

Short Title: The DISC study

STUDY SU/2006/2424
Protocol Version Number 1.1 20 June 2008
EUDRACT NO: 2006-006595-38

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the Final version of the protocol dated 20th April 2007 and entitled: 'A Phase II, Open-Label, Single-Arm Study to Assess the Efficacy and Safety of Decapeptyl® SR (3 mg and 11.25 mg formulations) when administered by subcutaneous injection'. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP) local regulations and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control who will be involved in the study.

Investigator Name: _____ **Title:** _____

Signature: _____ **Date:** _____

On behalf of the Sponsor:

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SYNOPSIS

Study Title:	Phase II, Open-Label, Single-Arm Study to Assess the Efficacy and Safety of Decapeptyl® SR (3 mg and 11.25 mg formulations) when administered by subcutaneous injection.
Study Objectives:	The purpose of this study is to evaluate the efficacy, safety and tolerability of Decapeptyl® SR when administered by subcutaneous (SC) injection. For the purpose of this study, patients will be considered to be responders if they achieve a Serum Total Testosterone Castration Level (STTCL), which is defined as a Serum Total Testosterone (STT) level of ≤ 50 ng/dL. **Primary Efficacy Study Objective** To evaluate the efficacy of Decapeptyl SR when given by SC injection in patients with prostate cancer. This will be determined by evaluating the proportion of patients who achieve STTCL 4 months after the first injection. **Secondary Study Objectives** 1. To evaluate the efficacy of an initial treatment with Decapeptyl SR 3 mg when given by SC injection. This will be determined by evaluating the proportion of patients who achieve STTCL 1 month after the first injection. 2. To evaluate the efficacy of a repeat treatment with Decapeptyl SR 11.25 mg when given by SC injection. This will be determined by evaluating the proportion of patients who achieve STTCL 1 month after the second injection. 3. To assess the changes in plasma triptorelin levels after administration of Decapeptyl SR by SC injection at all assessment time-points in comparison to Baseline. 4. To assess changes in the levels of Serum Total Testosterone (STT) and Prostate Specific Antigen (PSA), after administration of Decapeptyl SR via the SC route at all assessment time-points in comparison to Baseline. **Safety & Tolerability Objectives:** 1. To assess the safety of Decapeptyl SR when administered by SC injection. 2. To assess the tolerability of Decapeptyl SR when administered by SC injection.
Study Design:	This is an open-label, single-arm trial designed to assess the efficacy, safety and tolerability of Decapeptyl SR when administered by SC injection. Enrolled patients will be those who have a diagnosis of prostate cancer and for whom medical castration by means of LHRHa

	is indicated. Each patient's participation in the trial will last up 5 months (including Screening period). During the study, patients will receive one injection of Decapeptyl SR 3 mg (the 1-month sustained release formulation) and one injection of Decapeptyl SR 11.25 mg (the 3-month sustained-release formulation). The 3 mg injection will be administered at the study visit 2, on Day 0 (Baseline) and the 11.25 mg injection will be administered one month later, at visit 3. Patients will have additional follow-up visits at Month 2 and Month 4 (End of Study Visit). All visit dates will be calculated based on calendar months in order to ensure consistency with the recommended injection schedule for Decapeptyl SR. Written informed consent will be obtained from all patients prior to any study related procedures or assessments being performed. All study visits will begin between 09:00 and 11:00 hours as blood samples must be collected during this time window (due to possible diurnal variations in testosterone levels) Potential patients will be invited to attend a Screening visit (visit 1) for the study. At the Screening visit the following will be collected: • Informed consent. • Demographic details (date of birth, sex, ethnic origin, height, weight). • Relevant medical history. • Physical examination findings (including digital rectal examination (DRE) if this has not been done within 4 weeks prior to this visit). • Vital signs (height, weight, sitting blood pressure, pulse rate). • Blood samples (for analysis of serum total testosterone (STT), PSA, haematology and biochemistry). • Urine sample (for dipstick urinalysis). • Prior and concomitant medications. Patient's eligibility of the study will be checked by reviewing the inclusion and exclusion criteria. Eligible patients will then return to the clinic within the following month for the Baseline visit. At the Baseline visit: • Patients' eligibility for the study will be re-checked. • Blood samples will be collected for analysis of STT, PSA, plasma triptorelin and Liver Function Tests (LFTs) prior to receiving their injection. • Any adverse events or changes in concomitant medications since the Screening visit will be recorded. Patients who are still considered to be eligible for the study after completion of all Baseline assessments will then receive a SC injection of Decapeptyl SR **3 mg**. Subcutaneous injections should be

	administered into the anterior abdominal wall. Details of any immediate injection site reaction(s) will be recorded. To minimise risk of tumour flare, all patients will start adjuvant therapy with an anti-androgen, cyproterone acetate (CPA). Each patient will take 100 mg CPA, three times a day, for 2 weeks starting on the day of the Baseline visit. 24 hours after the injection, the site will call the patient to check whether there have been any tolerability issues following the injection. Details will be recorded in the patients CRF. One month after Baseline, patients will be required to attend the clinic for a follow up visit and repeat treatment (Visit 3). At this visit the following will occur: • Blood samples will be collected for analysis of STT, PSA, plasma triptorelin and liver function tests (LFTs). • Any new or altered adverse events or concomitant medications will be recorded. • Patients will then receive a SC injection of Decapeptyl SR **11.25 mg**. Subcutaneous injections should be administered into the anterior abdominal wall. Details of any immediate injection site reaction(s) will be recorded. 24 hours after the injection, the site will call the patient to check whether there have been any tolerability issues following the injection. Details will be recorded in the patients CRF. Patients will return to the clinic for a follow up assessment 2 months after the Baseline visit (visit 4). At this visit any new or altered adverse events or concomitant medications will be recorded. Blood samples will be collected (for analysis of levels of STT, PSA and plasma triptorelin). Four months after the Baseline visit, patients will return for an End of Study Visit (Visit 5) a physical examination will be performed and vital signs (weight, blood pressure, pulse rate) will be recorded. Blood samples will be collected (for analysis of levels of STT, PSA, plasma triptorelin, haematology and biochemistry). A dipstick urinalysis will be performed. Details of any new or altered adverse events or concomitant medications will be recorded. At the end of their study participation, patients will receive the standard medical care for their prostate cancer. This may involve treatment with Decapeptyl SR or any other marketed LHRHa at the discretion of the treating physician.
Study Population:	Approximately 50 patients will be enrolled in order to achieve 42 evaluable patients at the end of the study. Patients must satisfy the following eligibility criteria: **Inclusion Criteria** Patients must fulfil all of the following criteria in order to be included in the study:

	1. The patient has given written (personally signed and dated) informed consent before starting any study-related procedure, which means any assessment or evaluation that would not have formed part of their normal medical care. 2. The patient is male and is 18 years of age or older. 3. The patient has a histologically or cytologically confirmed diagnosis of prostate cancer and meets the following criteria: ▪ Stage T3 or T4, N (*any*), M (*any*) (see Appendix 1) with a PSA >5ng/ml or ▪ Biochemical relapse following radical prostatectomy or radical radiotherapy for prostate cancer 4. Medical castration by means of LHRHa therapy is indicated for the patient. 5. The patient has a life expectancy of at least 12 months. 6. The patient is able and willing to comply with the requirements of the protocol. **Exclusion Criteria** Patients who fulfil any of the following criteria, will not be included in the study: 1. The patient has undergone bilateral orchidectomy. 2. The patient is either scheduled to receive, receiving, or is anticipated to require any chemotherapy for prostate cancer, or any other cancer, during the period of his participation in the study. 3. The patient is either scheduled to receive, or anticipated to require any surgical intervention for their prostate cancer during the period of his study participation. 4. The patient has any condition that in the opinion of the Investigator may preclude the administration of subcutaneous Decapeptyl SR injections. 5. The patient has received treatment with any LHRHa within 1 year prior to study entry. 6. The patient has a history of hypersensitivity to Decapeptyl SR or CPA or to any of the excipients of Decapeptyl SR or CPA. 7. The patient has any contraindication to treatment with anti-androgens, including, but not limited to clinically significant abnormalities in liver function. 8. The patient has been treated with oestrogens or steroid androgens within the 12 months prior to screening, or is receiving treatment with non-steroid anti-androgens at the time of the Screening visit. 9. The patient, in the opinion of the Investigator is at risk of serious complications in the event of tumour flare (e.g. vertebral metastases threatening spinal cord compression, significant obstructive

	uropathy) on initiation of Decapeptyl SR treatment, despite concomitant treatment with anti-androgens. 10. The patient has any other condition that, in the opinion of the Investigator, might increase the risk to the patient or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study. 11. The patient is likely to require treatment during the study with drugs that are not permitted by the study protocol (For a list of drugs not permitted see Appendix 2). 12. The patient has received any investigational drug, within 30 days prior to the study or is scheduled to receive such a drug during the study. 13. The patient has a history of, or known current, problems with alcohol abuse. 14. The patient has any mental condition rendering him unable to understand the nature, scope and possible consequences of the study. 15. The patient has previously been enrolled in this study.
Study Treatment:	**Study Product:** Decapeptyl SR (triptorelin acetate) Decapeptyl SR (triptorelin acetate) is a micro-particle, sustained release LHRHa that is licensed for the treatment of advanced prostate cancer in the UK. The doses/formulations to be used in this study are within the constraints of the UK product licence: • Decapeptyl SR 3 mg (1-Month formulation). • Decapeptyl SR 11.25 mg (3-Month formulation). These formulations are already licensed in the UK for administration by intramuscular injection. Triptorelin (Gonapeptyl 3mg) is licensed for SC and IM administration. The treatment regimen in this study is consistent with the recommended treatment for prostate cancer in this patient population, as documented in the Summary of Product Characteristics (SPC) for Decapeptyl SR (see Appendix 3). The investigational product will not be used for purposes other than as defined in this protocol. Administration of the study drug will be performed by the Investigator, or study staff to whom this task has been delegated by the Investigator. Concomitant medication: Cyproterone Acetate 100mg three times daily, from Baseline Visit to Day 14.
Study Evaluations:	**Primary Efficacy Variables:** The proportion of patients with STT ≤50 ng/dL 4 months after their first injection of Decapeptyl SR. **Secondary Efficacy Variables:** Proportion of patients with STT ≤ 50 ng/dL 1 month after their first

	injection of Decapeptyl SR. Proportion of patients with STT ≤ 50 ng/dL 1 month and 3 months after the second injection of Decapeptyl SR. Plasma triptorelin levels at all assessment time-points. STT and PSA levels at all assessment time-points. **Safety Variables:** 1. Safety of subcutaneous route of administration will be assessed by examining the incidence of adverse events (AEs) and changes in concomitant medications at each assessment time-point. 2. Tolerability of the subcutaneous route of injection will be assessed by observation of the injection site and by means of a phone call 24 hours after each injection. Patients will provide feedback on the following parameters. • Pain (severity, time of onset in relation to the injection, duration). • Redness (severity, time of onset in relation to the injection, duration). • Swelling (severity, time of onset in relation to the injection, duration). Severity of injection site reactions will be graded using a 4 point scale (none, mild, moderate and severe).
Statistical Methods:	The trial will test the null hypothesis (H0) that the proportion of responders (defined as a patient who achieve STTCL (≤ 50 ng/dL) 4 months after the first injection is lower or equal to 80% against the alternative hypothesis H1 that the proportion of responders is larger or equal to 95%. We aim to show that the percentage of patients who achieve STTCL is larger than 80%: To achieve this, a total of 42 patients are needed and the cut-off for success is 39 patients who respond to treatment. Considering the method developed by A'Hern for exact calculation in single-stage phase II designs, a sample of 42 patients with a cut-off value fixed at 39 patients allows the rejection of the null hypothesis with an alpha-risk of 2% (one sided) and an 84% power. A drop out rate of up to 10% is anticipated and to accommodate withdrawals the study sample size has been increased to 47 patients in total. The primary endpoint will be test the null hypothesis H0 that the proportion of responders is lower or equal to 80% against the alternative hypothesis H1 that the proportion of responders is larger or equal to 95%. All variables analysed will be summarized in tables, which will include the descriptive statistics, as well as inferential statistics. The exact binomial test will be used for all analyses of proportions using a significance level of 0.025. 95% confidence intervals will be presented in all cases using Stata version 9.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

AE	Adverse Event
CPA	Cyproterone Acetate
CRF	Case Report Form
dl	Decilitre
DHT	Dihydroxytestosterone
DRE	Digital Rectal Examination
ETV	Early Termination Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GnRH	Gonadotrophin Releasing Hormone
ICH	International Conference on Harmonisation
IM	Intra-Muscular
IMP	Investigational Medicinal Product
ITT	Intention To Treat
LH	Luteinising Hormone
LHRH	Luteinising Hormone Releasing Hormone
LHRHa	Luteinising Hormone Releasing Hormone Analogue
MCV	Mean Cell Volume
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
ng	Nanogram
PP	Per Protocol
PSA	Prostate Specific Antigen
REC	Research Ethics Committee
SAE	Serious Adverse Event
SC	Subcutaneous
SPC	Summary of Product Characteristics
SR	Sustained Release
STT	Serum Total Testosterone
STTCL	Serum Total Testosterone Castration Level
SUSAR	Suspected Unexpected Serious Adverse Reaction

TEAE	Treatment Emergent Adverse Event
TNM	Tumor-Nodes-Metastasis (Staging System)
UHB	University Hospitals Bristol NHS Foundation Trust
WBC	White Blood Cell
Week	A week is defined as 7 days, i.e. Week 1 would equal Day 7, and Week 4 would equal Day 28.

2. BACKGROUND INFORMATION

2.1 Disease Review

Prostate cancer is a malignant tumour of the prostate gland. In most developed and developing countries, prostate cancer is the most commonly diagnosed malignancy affecting men beyond middle age, and is second only to lung cancer as a cause of cancer deaths in men [(1)].

The general prognosis remains poor with 70% survival at 10 years compared to the general population. About half of the cases are diagnosed at a locally advanced stage whilst about 30% present with bone metastases at the time of diagnosis [(1)].

Worldwide, there has been a consistent increase in the incidence of clinically significant disease in recent years. Moreover, because prostate cancer is primarily a disease affecting men over the age of 50 years, the worldwide trend towards an ageing population means the number of prostate cancer deaths is predicted to increase markedly during the next two decades.

Despite the high incidence of prostate cancer, relatively little is known about the fundamental causes of the disease. A number of risk factors have been established; age, race, diet, environmental factors, family history and hormone levels, all seem to have an influence over the development of cancer.

Testosterone and its more potent metabolite dihydroxytestosterone (DHT) are essential for normal prostate growth, and thus may play a part in the development of prostate cancer. Prostate cancer almost never develops in men castrated before puberty, or in individuals deficient in 5α reductase (the enzyme that converts testosterone to DHT). Although there is no correlation between circulating androgen concentrations and the risk of prostate cancer, a raised 5α reductase level may be associated with a higher incidence of the disease. At present the precise role of androgens and oestrogens in the development of prostate cancer remains to be established.

Most patients, in whom prostate cancer is suspected, are identified on the basis of abnormal findings on digital rectal examination (DRE) or, more commonly, by raised prostate specific antigen (PSA) levels. PSA is a glycoprotein responsible for liquefying semen. Approximately 20% of men with PSA levels above the normal range (≥4ng/dL) have prostate cancer, and the risk increases to more than 60% in men with PSA levels above 10ng/dL. These markers are very useful as, in general, the earlier prostate cancer is detected, the better the outlook for the patient.

Men with locally advanced or metastatic prostate cancer can present with a combination of symptoms:

- symptoms of bladder outflow obstruction such as frequency, hesitancy and poor flow,
- symptoms resulting from local extension of the tumour, such as haematuria or pain due to hydronephrosis secondary to obstruction of the ureters,
- symptoms resulting from distant metastases, such as low back pain, spinal cord compression, bone pain anaemia or weight loss.

There is a broad wealth of available treatment strategies for prostate cancer patients. The various treatments involve surgery and prostatic radiotherapy as

well as systemic treatments such as bisphosphonates and radionuclides in case of bone lesions, and hormonal treatments [2].

More recently, cytotoxic chemotherapy with a docetaxel-based regimen has been reported to significantly improve median survival of metastatic hormone refractory prostate cancer patients [3].

Under normal physiological conditions, the hypothalamus stimulates the pulsatile release of Luteinising Hormone Releasing Hormone (LHRH). This targets receptors on the anterior pituitary gland to stimulate both the synthesis and pulsatile release of the gonadotrophins; Luteinising Hormone (LH) and Follicle Stimulating Hormone (FSH). LH attaches to receptors on the Leydig cells of the testes promoting testosterone production, which is thought to play an essential role in prostate growth. It is thought therefore, that if testosterone levels are suppressed, the prostate gland growth may also be impeded, which would help in patients with abnormally growing prostate glands.

The hormone dependent nature of prostate cancer has formed the pathophysiological rationale for the hormone therapy of prostatic carcinoma and the introduction of LHRH analogues (LHRHa's) into the therapeutic armamentarium has revolutionised the treatment of advanced prostate cancer [4].

LHRHa (also known as Gonadotrophin Releasing Hormone analogues (GnRHa) work by mimicking the physiological actions of LHRH. The analogues have a much longer half life than naturally occurring LHRH. This results in a down-regulation of receptors in the pituitary, an inhibition of FSH/LH production and a significant decrease in testosterone production, after a transitory phase of hyper-stimulation; in effect inducing medical castration.

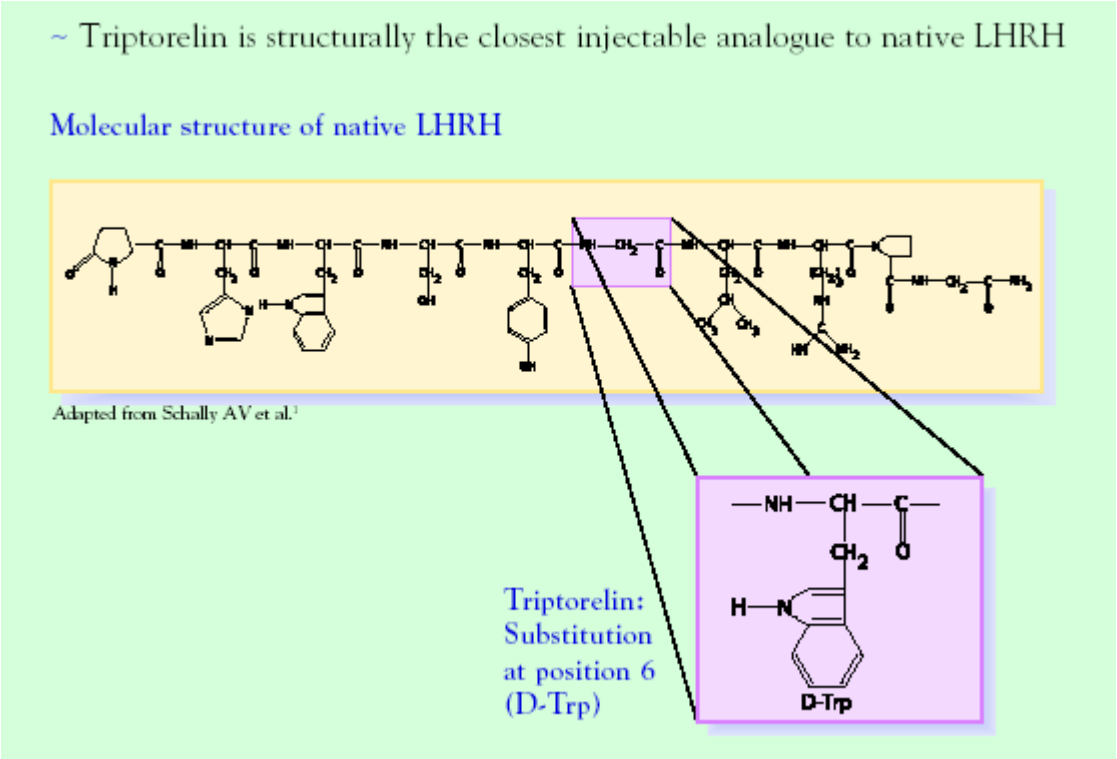
Medical castration, by administration of LHRHa, reduces the intraprostatic concentration of DHT by over 80%; which is comparable to surgical orchidectomy (surgical removal of the testes; castration). This has huge advantages both physically and psychologically to the patients.

Achieving and maintaining serum testosterone at castration levels are the main goal of therapy with LHRHa [5]. Typically the serum total testosterone castration level (STTCL) is set at 50 ng/dL. Whilst there is some suggestion that the lower the serum total testosterone level, the better, this suggestion is still the subject of debate and lower castrate levels are not widely used as a treatment target in the UK.

2.2 Compound Review

Structurally, Decapeptyl® SR (triptorelin) is the closest LHRHa to native LHRH, with just a single amino acid substitution (Gly is substituted for D-Trp at position 6 of the structure).

Table 1Molecular structure of Triptorelin



The substitution enhances resistance to enzymatic degradation and increases receptor binding affinity. LHRHa differ from each other in their relative potencies and plasma half-lives. Decapeptyl SR is 100 times more potent that native LHRH. It is also more potent than other commonly used LHRHa's. Decapeptyl SR also has a longer half life than both native LHRH and other commonly used LHRHa.

Decapeptyl SR, the first sustained release injectable decapeptide super-analogue was launched in France in 1983. Sustained release formulations of Decapeptyl SR given by intra muscular (IM) injection are widely approved for use. Decapeptyl SR has been used for more than 12 million treatment months across Europe since its launch.

Decapeptyl SR is licensed for the treatment of advanced prostate cancer.

Tumour flare, caused by the initial hyper-stimulation of pituitary receptors, has been reported in about 5% of patients[(6)] and is preventable with the administration of an anti-androgen around the time of introduction of LHRHa treatment.

2.3 Clinical Trial Rationale

In the UK, Decapeptyl SR is marketed as a palliative treatment for patients with advanced prostate cancer. Both the 3mg and 11.25 mg formulations are licensed in the UK for administration by IM injection.

If Decapeptyl SR is as effective when given by subcutaneous injection as when given by intramuscular injection then this would offer patients a greater choice of injection sites and facilitate ease of patient self injection.

There is limited data available on the administration of triptorelin by sub-cutaneous (SC) injection, however, studies performed to date, have demonstrated that triptorelin is as effective safe and well tolerated when injected by SC injection as it is when given by IM injection in patients with prostate cancer. (Klippel *et al.* [7])

An ongoing pharmacokinetic study to evaluate 2 different 4-Month formulations of Decapeptyl includes a study arm (12 patients) in which patients receive Decapeptyl SR 15 mg, (as triptorelin acetate) injected by the SC route. Preliminary results demonstrate that the proportion of responders and the time taken to achieve STTCL is similar to results obtained in previous studies evaluating administration of triptorelin acetate via the IM route (data on file, Ipsen).

There are other similar Sustained Release (or Depot) LHRHa available in the UK that are licensed for both SC and IM injection. These include leuprorelin acetate (Prostap® SR, Wyeth) and another brand of triptorelin acetate (Gonapeptyl Depot).

The purpose of this study therefore is to evaluate the efficacy, safety and tolerability of Decapeptyl SR when administered by subcutaneous (SC) injection in order to provide greater patient choice in method and site of injection. In accordance with usual treatment practice in the UK, the main objectives of this study are to achieve and maintain STTCL. For the purpose of this study STTCL is defined as a serum total testosterone level of ≤ 50 ng/dL

2.4 Primary Objective

To evaluate the efficacy of Decapeptyl SR when given by SC injection in patients with prostate cancer. This will be determined by evaluating the proportion of patients who achieve STTCL 4 months after the first injection.

2.5 Secondary Objectives

To evaluate the efficacy of an initial injection with Decapeptyl SR 3mg when given by SC injection. This will be determined by evaluating the proportion of patients who achieve STTCL 1 month after the first injection.

To evaluate the efficacy of a repeat injection with Decapeptyl SR 11.25mg when given by SC injection. This will be determined by evaluating the proportion of patients who achieve STTCL 1 month after the second injection.

To assess changes in plasma triptorelin levels after administration of Decapeptyl SR by SC injection at all assessment time-points in comparison to Baseline.

To assess changes in the levels of Serum Total Testosterone (STT) and Prostate Specific Antigen (PSA), after administration of Decapeptyl® SR by SC route injection at all assessment time-points in comparison to the Screening visit.

3. STUDY DESIGN

3.1 Study Design

This is an, Open-Label, Single-Arm study.

3.2 Study Population

Approximately 50 patients with prostate cancer who satisfy the inclusion / exclusion criteria will be recruited into the study from routine clinics and within secondary care referrals.

3.3 Study Duration

Up to 1 month after Screening, eligible patients will return for the Baseline visit and will receive 4 months treatment with Decapeptyl SR.

Each patient's participation in the trial will last up to 5 months (including Screening period).

3.4 Study Schedule

Table 2Study Schedule

a) Assessment	**Visit 1 - Screening**	**Visit 2 - Baseline**	**Visit 2a (phone)**	**Visit 3**	**Visit 3a (phone)**	**Visit 4**	**Visit 5 /ETV**
Month (visits calculated using calendar months)	**≤ 1 mth before D0**	**DAY 0**	**V2 + 1 Day**	**M1 (± 3 days)**	**V3 + 1 Day**	**M2 (± 3 days)**	**M4 (± 3 days)**
Written Informed Consent	✓						
Review Inc/ Exc Criteria	✓	✓					
Record Demographics	✓						
Record Medical History (inc. prostate cancer)	✓						
Digital Rectal Examination	✓[1]						
Physical Examination	✓						✓
Vital Signs	✓	✓		✓		✓	✓
Blood Samples (serum total T, PSA)[2]	✓	✓		✓		✓	✓
Blood samples (haematology & biochemistry)	✓			✓ (LFTs only)			✓
Blood sample for plasma triptorelin		✓		✓		✓	✓
Dipstick Urinalysis	✓						✓
Start 2wks tx with Anti-Androgen (CPA)		✓					
Decapeptyl SR injection[3]		✓ (3mg)		✓ (11.25mg)			
Injection tolerability assessment		✓	✓ (24hrs after injection)	✓	✓ (24hrs after injection)		
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓	✓	✓	✓
End of Study Record							✓

3.5 Study Visits

3.5.1 Visit 1 - Screening (within 4 weeks prior to Baseline) – For ALL Patients

Potential study patients will be identified from clinics at the study site and either approached during routine clinic appointments, or in writing about the study.

[1] If the patient has had a DRE within 4 weeks of the Screening visit, this does not need to be repeated.
[2] Blood samples are to be collected between 09:00 and 11:00hrs.
[3] Decapeptyl SR injections to be administered after all study procedures have been completed.

Referrals may be sought from within secondary care. Local patient support groups may be made aware of the study as applicable.

Suitable patients will be invited to attend the clinic for a Screening visit between 2 days and 4 weeks prior to the Baseline visit. Written informed consent will be obtained prior to any study related assessments or procedures being performed. The visit will take place between 09:00 and 11:00 hours as the blood samples must be collected within this time-frame (due to the possibility of diurnal variations in testosterone levels). The following assessments and procedures will be completed at this visit:

- Patient's eligibility for the study will be checked by reviewing the inclusion and exclusion criteria.
- Demographic details (date of birth, ethnic origin, height, weight).
- Relevant medical and surgical history, including current medical conditions. This will include their history of prostate cancer, TNM staging, Gleason score and PSA.
- Physical examination findings (including digital rectal examination (DRE) if this has not been done within 4 weeks prior to this visit).
- Vital signs (height, weight, blood pressure and pulse rate). Blood pressure and heart rate should be recorded sitting, after the patient has been seated at rest for 5 minutes.
- Blood samples (for analysis of serum total testosterone (STT), PSA, haematology and biochemistry). These samples should be collected between 09:00 and 11:00 hours.
- Urine sample (for dipstick urinalysis). In the even of any significant findings on urinalysis, further investigations should be performed at the discretion of the Investigator.
- Prior and concomitant medications.
- An appointment will be made for eligible patients to return to the clinic for the Baseline visit up to 1 month later.

3.5.2 Baseline (Week 0)

Eligible patients will return to the clinic within the following month for the Baseline visit. At the Baseline visit:

- Patients' eligibility for the study will be re-checked.
- Blood samples will be collected for analysis of STT, PSA and plasma triptorelin prior to dosing.
- Any adverse events or changes in concomitant medications since the Screening visit will be recorded.

Patients who are still considered to be eligible for the study after completion of all Baseline assessments will then receive a SC injection of Decapeptyl SR 3 mg. Subcutaneous injections should be administered into the anterior abdominal wall. Details of any immediate injection site reaction(s) will be recorded.

To minimise risk of tumour flare, all patients will start adjuvant therapy with an anti-androgen, cyproterone acetate (CPA). Each patient will take 100 mg CPA, three times a day, for 2 weeks starting on the day of the Baseline visit.

24 hours after the injection, the site will call the patient to check whether there have been any tolerability issues following the injection. Details will be recorded in the patients CRF. Patients will provide feedback on:

- Pain (severity, time of onset in relation to the injection, duration).
- Redness (severity, time of onset in relation to the injection, duration).
- Swelling (severity, time of onset in relation to the injection, duration).
- Severity of injection site reactions will be graded using a 4 point scale (none, mild, moderate and severe).

3.5.3 Visit 3 (month 1)

One month after the Baseline visit (+/- 3 days), patients will be required to attend the clinic for a follow up visit and their second injection. (Visit 3). At this visit the following will occur:

- Blood samples will be collected for analysis of STT, PSA, plasma triptorelin and liver function tests (LFTs).
- Any new or altered adverse events or concomitant medications will be recorded.

Patients will then receive a SC injection of Decapeptyl SR 11.25 mg. Subcutaneous injections should be administered into the anterior abdominal wall. Details of any immediate injection site reaction(s) will be recorded.

24 hours after the injection, the site will call the patient to check whether there have been any tolerability issues following the injection. Details will be recorded in the patients CRF.

3.5.4 Visit 4 (month 2)

Patients will return to the clinic for visit 4 (day 84) Visits can be +/- 3 days.

At each study visit any adverse events or changes in concomitant medications since the previous visit will be recorded. At all visits, blood samples will be taken for analysis of levels of STT, PSA, and plasma triptorelin.

3.5.5 Visit 5 (day 112:) Study Completion / Early Termination Visit

Patients will return to the clinic 4 months after the Baseline visit for the study completion visit. If a patient discontinues from the study prematurely, every effort should be made to perform an early termination visit, including the assessments listed here.

- Vital signs
- Urinalysis
- Blood samples for STT, PSA, plasma triptorelin, haematology and biochemistry
- Concomitant Medication and adverse events

At the patient's last study visit details of their completion of the study / withdrawal from the study will be recorded. At the end of the study patients will

receive the standard medical care for their prostate cancer. This may involve treatment with Decapeptyl SR or another marketed LHRHa at the discretion of the treating physician.

4. SELECTION & WITHDRAWAL OF SUBJECTS

4.1 Patient Selection Criteria

4.1.1 Inclusion criteria

Patients must satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. The patient must give written (personally signed and dated) informed consent before starting any study-related procedure, which means any assessment or evaluation that would not have formed part of their normal medical care.
2. The patient is male and is 18 years of age or older.
3. The patient has a histologically or cytologically confirmed diagnosis of prostate cancer and meets the following criteria:
    - Stage T3 or T4, N (*any*), M (*any*) (see Appendix 1) with a PSA >5ng/ml or
    - Biochemical relapse following radical prostatectomy or radical radiotherapy for prostate cancer
4. Medical castration by means of LHRHa therapy is indicated for the patient.
5. The patient has a life expectancy of at least 12 months.
6. The patient is able and willing to comply with the requirements of the protocol.

4.1.2 Exclusion Criteria

Patients who satisfy any of the following criteria must not be included in the study:

1. The patient has undergone bilateral orchidectomy.
2. The patient is either scheduled to receive, receiving or anticipated to require any chemotherapy for prostate cancer or any other cancer during the period of his participation in the study.
3. The patient is either scheduled to receive, or anticipated to require any surgical intervention for their prostate cancer during the period of his study participation.
4. The patient has any condition that in the opinion of the Investigator may preclude the administration of subcutaneous Decapeptyl SR injection.
5. The patient has received treatment with any LHRHa within one year prior to study entry.
6. The patient has a history of hypersensitivity to Decapeptyl SR or CPA and any of their excipients.
7. The patient has any contraindication to treatment with anti-androgens, including, but not limited to clinically significant abnormalities in liver function.

8. The patient has been treated with oestrogens or steroid androgens within the 12 months prior to screening, or is receiving treatment with non-steroid anti-androgens at the time of the Screening visit.
9. The patient, in the opinion of the Investigator, is at risk of serious complications in the event of tumour flare (e.g. vertebral metastases threatening spinal cord compression, significant obstructive uropathy) on initiation of Decapeptyl SR treatment despite concomitant treatment with anti-androgens.
10. The patient has any other condition that, in the opinion of the Investigator, might increase the risk to the patient or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.
11. The patient is likely to require treatment during the study with drugs that are not permitted by the study protocol (See Appendix 2).
12. The patient has received any investigational drug therapy within 30 days prior to study entry, or is scheduled to receive such a drug during the study period.
13. The patient has a history of, or known current, problems with alcohol abuse.
14. The patient has any mental condition rendering him unable to understand the nature, scope and possible consequences of the study.
15. The patient has previously been enrolled in the study

4.2 Patient Withdrawal Criteria

If one or more of the following occurs, the patient will be withdrawn from the study:

- Patient decision to withdraw from the trial.
- Initiation of any oestrogen, any LHRHa (other than the Decapeptyl SR prescribed for this study) or any antiandrogen (other than the cyproterone acetate two week treatment as described in this protocol).
- Unacceptable safety or tolerability as determined by the Investigator.
- Concurrent, non-cancer related reason, which prevents regular follow up of the patient.
- General or specific changes in the patient's condition, which, in the Investigator's judgement, requires medical intervention and prohibits the patient from compliance with the protocol procedures.

If a patient discontinues from the study prematurely (i.e. prior to completion of the protocol), the primary reason for discontinuation will be determined and recorded. In all cases the Investigator will ensure that the patient receives medical follow-up as necessary.

Patients who withdraw from the study will not be replaced. Under no circumstances will patients be enrolled more than once.

5. STUDY TREATMENT

5.1 Study Medication

Decapeptyl SR 11.25 mg (triptorelin acetate) is presented as a powder for suspension for injection in a sustained release formulation. Each 4 ml glass vial contains 15 mg of Triptorelin acetate plus excipients. The overage is to ensure that a dose of 11.25 mg is administered to the patient. Also supplied is a 3 ml glass ampoule containing 2 ml of mannitol solution 0.8% for injection, which is the suspension vehicle for Decapeptyl SR.

Decapeptyl SR 3mg (triptorelin acetate) is presented as a powder for suspension for injection in a sustained release formulation. Each glass vial contains 4.2mg of Triptorelin acetate plus excipients. The overage is to ensure that a dose of 3 mg is administered to the patient. Also supplied is a 3 ml glass ampoule containing 2 ml of mannitol solution 0.8% for injection. The suspension for injection must be reconstituted following the aseptic technique and using the provided ampoule of mannitol solution 0.8% for injection.

The suspension vehicle should be drawn into the syringe provided using the pink needle and transferred to the vial containing the powder for injection. The vial should be gently shaken and the mixture then drawn back into the syringe without inverting the vial. The needle should then be changed before administering the injection.

Decapeptyl SR should be reconstituted immediately prior to injection.

5.2 Supply of Study Medication

Commercially available supplies of medication will be used for this clinical Study. It is the responsibility of the sponsor to ensure study treatment is re-labelled to comply with Annex 13 of the Rules Governing Medicinal Products in the European Union.

5.3 Study Treatment Administration

Study medication will be reconstituted as described above.

Decapeptyl SR 3mg and 11.25mg should be administered by sub-cutaneous injection into the anterior abdominal wall.

5.4 Study Treatment Labelling

The core label texts for all packaging units will comply with the requirements of Annexe 13 of the Rules Governing Medicinal Products in the European Union, and the national laws in force in the UK.

A description of the core text of the IMP labels is displayed below:

- Sponsor name
- Study Number
- Pharmaceutical dosage form
- Route of administration
- Quantity of dose units
- Batch number
- For clinical trial use only'
- 'Keep out of reach of children'

- Name, address and telephone number of the Sponsor, or Investigator (the main contact for information on the product and clinical trial)
- Storage conditions
- Expiry date

5.5 Study Treatment Storage and Accountability

The product should not be stored above 25°C. It should be kept in the container in the outer carton.

Study medication will be stored and dispensed by the trial site's pharmacy department in accordance with Good Clinical Practice and Good Manufacturing practice.

Records will be maintained of the accountability of all study treatments and all used and unused supplies must be retained for verification and drug accountability.

5.6 Compliance

Compliance will be monitored by recording scheduled and actual injection dates and other relevant information on a treatment administration record. All used and unused medication vials and packaging (excluding sharps) will be retained by the Investigator or designee in order to verify compliance.

5.7 Concomitant Medications

All concomitant medications taken during the study will be recorded in the patients CRF. The use of dietary and herbal supplements during the study is not prohibited. All such supplements will be recorded in the concomitant medications page of the patients CRF.

The following concomitant medications are not allowed during the patient's study participation:

- Any medications which raise prolactin levels.
- Any LHRHa other than the Decapeptyl SR prescribed for this study.
- Any other oestrogens or androgens.
- Any anti-androgen from the end of second week after the study Baseline visit.

Changes in concomitant medications taken during the study will be documented.

6. STUDY EVALUATIONS

6.1 Clinical Laboratory Tests

Clinical laboratory tests will be performed by the UHB Pathology Department, Level 9 Queens Building, Bristol Royal Infirmary, Bristol BS2 8HW. Details of the methodology and reference ranges will be kept in the Trial Site File. Laboratory test results will be recorded on the laboratory results pages of the CRF. All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to Baseline or to a level deemed acceptable by the Investigator or until the abnormality is explained by an appropriate diagnosis.

The total blood during the whole course of the study, taken for serology, biochemistry, haematology, testosterone and PSA will not exceed 75 mL per patient

Blood samples for clinical laboratory tests will be taken at the specified study visits and will consist of the following

Haematology: approx 5mL blood will be collected into a potassium Ethylenediamine Tetra-acetic Acid (EDTA) anticoagulant tube. Parameters to be assessed will include:

- Haemoglobin
- Haematocrit
- Mean cell volume (MCV)
- Mean cell haemoglobin (MCH),
- Mean cell haemoglobin concentration (MCHC)
- White blood cell (WBC) count with differential
- Platelet count.

Biochemistry: approx 5mL blood will be collected into an SST or PST tube. Parameters to be assessed will include:

- Creatinine
- Urea
- Sodium
- Potassium
- Bilirubin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Total protein
- Albumin
- Globulin
- Calcium
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl transferase (GGT)
- Total cholesterol
- Triglycerides

Urine analysis (fresh urine): A dipstick analysis of pH, protein, ketones, glucose, bilirubin, blood, urobilinogen and specific gravity will be performed. Further testing (e.g., microscopy and culture) will be carried out at local laboratory at the discretion of the Investigator. Should any clinically significant finding such as infection be noticed, this should be recorded as an Adverse Event and any treatment should be recorded on the CRF concomitant medications page.

6.1.1 Serum Total Testosterone

Venous blood samples will be collected for analysis of serum total testosterone by direct venous puncture at Baseline and Week 4.

Due to the possibility of diurnal variation of serum testosterone levels, blood samples to assess testosterone level should be drawn in the morning between 9:00 and 11:00hrs. Blood samples will be collected into an SST or PST tube and transferred to the lab at ambient temperature.

6.1.2 Prostate Specific Antigen (PSA),

Venous blood samples will be collected for analysis of PSA at all study visits. Blood samples will be collected into an SST or PST tube and transferred to the lab at ambient temperature.

6.1.3 Plasma Triptorelin,

Blood samples will be collected for analysis of plasma triptorelin levels at all study visits from screen onwards.

Blood samples will be collected into 5 ml Vacutainer tubes (containing EDTA and aprotinin), and will be centrifuged at 4°C at 2000 g for 15 minutes. The plasma will be rapidly transferred to two polystyrene tubes. The tubes will be stoppered (airtight) and stored at -20°C. Samples will be transferred in batches to Ipsen Pharma S.A and will be analysed by Ipsen Pharma S.A.

The analytical method that will be used to determine triptorelin in plasma samples is based on a radioimmunoassay (RIA) procedure, previously validated in the experimental conditions used at Ipsen Pharma S.A[8]. The limit of quantification of the assay is 0.010 ng/ml .

6.2 Safety Evaluations

6.2.1 Injection Tolerability

Following each injection patients will be asked about any injection site reactions. Patients will provide feedback 24 hours post-injection which will be recorded in the patients CRF.

The following parameters will be assessed:

- Pain (severity, time of onset in relation to the injection, duration).
- Redness (severity, time of onset in relation to the injection, duration).
- Swelling (severity, time of onset in relation to the injection, duration).

Severity of injection site reactions will be graded using a 4 point scale (none, mild, moderate and severe).

6.2.2 Adverse events.

All adverse events will be reported in accordance with the UHB adverse event policy.

An adverse event is any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily related to that product.

An Adverse Event can therefore be any unfavourable and unintended sign (including abnormal lab results), symptom (such as nausea, fatigue) or disease temporally associated with the use of the medicinal product whether or not considered to be related to the medicinal product.

Pre-existing conditions that worsen during a study are to be reported as adverse events.

When the deterioration in the condition for which the study drug is being used (i.e., disease progression) is interpreted as a natural outcome of the disease, it should not be recorded as an Adverse Event.

This definition includes events occurring from the time of patient giving informed consent until the end of the study.

The safety of Decapeptyl SR by the SC route in the treatment of patients with prostate cancer will be evaluated by examining the occurrence of all adverse events, abnormal laboratory findings, the use of concomitant medications and physical examination findings

6.3 Categorisation of Adverse Events

6.3.1 Intensity Classification

Adverse events will be classified as mild, moderate or severe according to the following criteria:

- Mild: an event that is easily tolerated by the patient causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

6.3.2 Causality Classification

The relationship between the drug and the occurrence of each adverse event will be assessed and categorised as below. The Investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying disease, concomitant therapy, other risk factors etc will be considered. The Investigator will also consult eh Investigator Brochure or other product information.

Not related: Temporal relationship of the onset of the event relative to the administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

Unlikely: Temporal relationship of the onset of the event, relative to the administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.

Possibly related: Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable but the event could have been due to another equally likely cause.

Probably related: Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.

Definitely related: Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and there is no other cause to explain the event or a re-challenge (if feasible) is positive.

6.3.3 Expectedness

Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined according to the

reference documents as defined in the study protocol (e.g. Investigator brochure or marketing information).

Expected: Reaction previously identified and described in the summary of product characteristics (SmPC).

Unexpected: Reaction not previously described in the protocol or reference documents.

6.3.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values will only be reported as adverse events if any of the following apply:

- they result in a change in study drug schedule of administration (change in dosage, delay in administration, study drug discontinuation),
- they require intervention or a diagnosis evaluation to assess the risk to the patient,
- they are considered as clinically significant

6.3.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as adverse events.

6.3.6 Other investigation abnormal findings

In addition, abnormal objective test findings that result in a change in study drug dosage or administration schedule, or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the patient, should be recorded as adverse events.

6.3.7 Recording and Follow-up of Adverse Events

At each visit the patient should be asked a non-leading question such as: "Do you feel different in any way since starting the new treatment/the last assessment?"

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the adverse event page(s) of the CRF using the standard UHB reporting forms. Adverse events already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all adverse events, the Investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Sponsor. For all adverse events, sufficient information should be obtained by the Investigator to determine the causality of the adverse event (i.e., study drug or other illness). The Investigator is required to assess causality and record that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.

Annual safety reports will be sent to the Sponsor, the main REC and the MHRA.

6.4 Serious Adverse Events

6.4.1 Definitions

All serious adverse events (as defined below) regardless of any suspected relationship to the study drug must be reported immediately to the sponsor. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A serious adverse event is any adverse event occurring at any dose that:

1. results in death;
2. is life threatening.(that is any event that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death)
3. results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons
4. results in a persistent or significant disability or incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
5. results in congenital anomaly or birth defect in the offspring of a patient who received the study drug;

Initial hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.

Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician. Prolongation in the absence of a precipitating, treatment-emergent, clinical adverse event (i.e. not associated with the development of a new adverse event or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor. Pre-planned treatments or surgical procedures should be noted in the Screening documentation for the entire protocol and/or for the individual patient. Hospitalisation for a procedure related to the disease under investigation (e.g. puncture of effusion), is not to be considered as a serious adverse event.

6.4.2 Reporting Requirements

Within 24 hours of a member of the research team becoming aware of a serious adverse event the Sponsor must be notified. The Investigator (or delegated person) will make an initial report, orally or in writing. Oral reports will be followed up in writing within 24 hours of the initial report. Written reports will be made by completing the UHB SAE/SUSAR reporting form. (Appendix 4). The initial report will include as much information as is available at the time.

Investigators (or delegated persons) will provide follow-up information, each time new information is available, using the UHB Research Related SAE/SUSAR Follow-up Report form (Appendix 4), until the SAE has resolved or a decision for no further follow up has been taken.

The Chief Investigator will provide the main REC with copies of all reports and recommendations of any independent Data Safety Monitoring Board established for a trial. A written acknowledgement is required from the main REC to confirm that they have received this notification.

6.4.3 Mandatory Information for Reporting an SAE

The following information is the minimum that must be provided to the sponsor pharmacovigilance contact within 24 hours for each SAE:

- Trial number
- Centre number
- Patient number
- Adverse event
- Seriousness criteria with immediate outcome
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. Upon receipt of the initial report, the sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator is encouraged to report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary adverse event considered as the foremost untoward medical occurrence from secondary adverse events which occurred as complications.

6.4.4 Follow-up of Serious Adverse Events

Serious adverse events, especially those for which the relationship to drug is different from "not related" should be followed up until they have returned to Baseline status or stabilised at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.

If a clear explanation is established for the relationship assessment it should be recorded on the CRF.

6.5 Deaths

All deaths occurring during the study, or within 28 days after the last dose of study drug, must be reported as a SAE within 24 hours. However, deaths due unequivocally to progression of disease are not to be considered as SAEs.

7. INFORMED CONSENT

7.1 Informed Consent

The Investigator, or a person designated by the Investigator, will explain the benefits and risks of participation in the study to each patient and obtain written informed consent.

Written informed consent will be obtained prior to the patient entering the study (before initiation of any study-related assessment or procedure and before administration of study drug). The final, version dated, form must be approved by the REC. Each patient's original consent form, personally signed and dated by the subject and by the person who conducted the informed consent discussion, will be filed in the patients medical notes. The Investigator will supply all enrolled patients with a copy of their signed informed consent and the patient

information sheet. A copy of the signed consent form will be kept in the study site file.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the patient. In this instance approval should always be given by the REC and existing patients informed of the changes. This is documented in the same way as previously described.

With the consent of the patient the patient's GP will be notified of their participation in the trial.

8. STATISTICAL CONSIDERATIONS

8.1 Subject Classification and Definitions

- **Enrolled subject:** Subject fully informed about the study who has given written informed consent to participate (before any occurrence of trial related procedure)
- **Screened failure subject:** Enrolled subject who fails to fulfil one or more entry criteria and thus does not proceed to the treatment phase of the study. Although not exposed to study medication, they may have been exposed to some study related procedures. Records up to the time of premature termination should be completed including the reason for termination
- **Treated subject :** Enrolled subject who is treated with at least one dose of study medication
- **Treatment Completed subject:** Treated subject who has completed all specified phases/assessments of the active treatment.
- **Study Completed subject:** Treated subject who has completed all specified phases/assessments of the study.
- **Drop-out:** Treated subject who did not complete the study and or treatment.

8.2 Analyses Populations Definitions

- **Screened population**: All subjects enrolled
- **Safety population**: All subjects who received at least one injection of study medication .
- **Intention-to-treat (ITT) population**: All treated subjects
- **Per protocol (PP) population**: All subjects in the ITT population for whom no major protocol violations / deviations occurred

8.2.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint(s) will be performed on the ITT population. In addition, a secondary analysis will be performed using the PP population.

All secondary analyses will be carried out using the ITT population.

The analyses of safety data will be performed based on the Safety population.

The rules for the allocation of subjects to each of the analysis populations will be defined and documented during a data review meeting held prior to database lock.

During the data review meeting, based on minor or major protocol violations / deviations, subjects may be excluded from the ITT/PP populations.

8.3 Sample Size Determination

The trial will test the null hypothesis (H0) that the proportion of responders (defined as a subject who achieve STTCL (< 50 ng/dL) 4 months after the first injection is lower or equal to 80% against the alternative hypothesis H1 that the proportion of responders is larger or equal to 95%.

Considering the method developed by A'Hern for exact calculation in single-stage phase II designs, a sample of 42 subjects with a cut-off value fixed at 39 subjects allows the rejection of the null hypothesis with an alpha-risk of 2% (one sided) and an 84% power. A drop out rate of up to 10% is anticipated and to accommodate withdrawals the study sample size has been increased to no more than 50 subjects in total.

8.3.1 Significance Testing and Estimations

Statistical tests for the primary efficacy criterion will be performed one sided with a type I error rate set at 2.5%.

8.4 Statistical/Analytical Methods

Statistical analyses will be performed by staff from the Bristol Research and Development Support Unit. Statistical evaluation will be performed using SPSS and Stata.

8.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, SD, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease pre-treatment AEs and on-going medical history, prior medications, baseline symptoms) will be presented for the ITT population.

8.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in the ITT/PP and safety populations will be tabulated by centre. The reasons for subject exclusions from each of the populations will also be tabulated. Primary reasons for discontinuation of study treatment will be tabulated.

8.4.3 Efficacy Evaluation

Primary Endpoint

The primary endpoint will be test the null hypothesis H0 that the proportion of responders (defined as subject who achieve STTCL (< 50 ng/dL) 4 months after

the first injection) is lower or equal to 80% against the alternative hypothesis H1 that the proportion of responders is larger or equal to 95%.

The secondary endpoints are:

- Proportion of subjects who achieve STTCL 1 month after the first injection.
- Proportion of subjects who achieve STTCL 1 month after the second injection.
- Changes in plasma triptorelin levels after administration of Decapeptyl SR by SC injection at all assessment time-points in comparison to Baseline.
- Changes in the levels of Serum Total Testosterone (STT) and Prostate Specific Antigen (PSA), after administration of Decapeptyl® SR by SC route injection at all assessment time-points in comparison to the Screening visit
- Changes in plasma triptorelin levels after administration of Decapeptyl SR at all assessment time-points from week 4.

Summary tables will be provided with the number and percentage of subjects with STTCL 1 month after the first and the second injection. Exact binomial 95% confidence intervals of proportions will also be provided. Descriptive statistics (N, Mean, SD, Median, Minimum and Maximum) as well as 95% confidence intervals will be calculated for STT / PSA / Plasma triptorelin levels at each timepoint and for changes from baseline and week 4 as relevant.

8.4.4 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

AEs will be coded according to the National Cancer Institute Common Terminology for Adverse Events Version 3.0

Incidence of all reported AEs/TEAEs and SAEs will be tabulated. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.

A treatment emergent AE (TEAE) is defined as any AE that occurs during the active phase of the study if:

it was not present prior to receiving the first dose of IMP, or

it was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study, or

it was present prior to receiving the first dose of IMP, the intensity is the same but the drug relationship became possible or probable during the active phase of the study.

Treatment emergent AEs will be flagged (*) in the AEs listings.

Concomitant medication will be summarised by treatment group and by overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, standard deviation (SD) and range as appropriate) by treatment group and by overall will be presented for vital signs, clinical laboratory tests at each assessment with change from baseline. For

laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Tables will be presented of the number and percentage of subjects with low, normal or high values.

8.5 Interim Analyses and Data Monitoring

An interim number of treatment failures will be recorded. If this number reaches 6 or more recruitment will be closed and a data monitoring committee will be convened.

9. COMPLIANCE WITH GCP & ETHICAL CONSIDERATIONS

The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval.
This study will be conducted in accordance with:
• The Medicine for Human Use (Clinical Trials) Regulations 2004.
• International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
• Research Governance Framework for Health and Social Care.

Monitoring and Audit

The study will be subject to monitoring and audit in accordance with UHB policy. All trial related documents will be made available on request for monitoring and audit by UHB, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies.

10. DATA HANDLING AND RECORD KEEPING

The Investigator is to report all data with respect to protocol procedures, drug administration, laboratory data, safety data and efficacy data in the patients' medical records in addition to any study specific forms.

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 15 years following the end of the study. Where trial related information is documented in the medical records those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 15 years after the last patient last visit.

11. INDEMNITY

This is an NHS sponsored research study. For NHS sponsored research HSG(96)48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

12. FINANCE

This study is funded by a grant from IPSEN. The grant will cover the cost of the trial including research clinic staff time (trial research nurse and research fellow), pharmacy dispensing costs and the costs of laboratory tests. Patients will not be paid for their involvement in the study but travel expenses to and from research outpatient clinics will be paid.

13. DISSEMINATION OF RESULTS

The results of this study will be published in peer-reviewed journals and made available to prostate cancer and mens health groups.

14. REFERENCES

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[5] Tombal B, Appropriate Castration with Luteinising Hormone Releasing Hormone (LHRH) Analogues: What is the Optimal Level of Testosterone?; European Urology Supplements 4 (2005) 14-19

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[8] Ipsen Pharma S.A. Internal report 96/PKS/010. Validation of radioimmunoassay of triptorelin in human plasma. July 2001

APPENDIX 1 TNM STAGING

TNM Classification System (T)

TX Primary tumor cannot be assessed
T0 No cancer detected
T1 Clinically inapparent tumor–not palpable or visible by imaging
T1a Tumor found incidentally; takes up < 5% of prostate tissue
T1b Tumor found incidentally; takes up > 5% of prostate tissue
T1c Tumor identified by prostate needle biopsy because of elevated PSA
T2 Palpable tumor confined within the prostate
T2a Tumor involves < 50% of 1 prostate lobe
T2b Tumor involves > 50% of 1 prostate lobe
T2c Tumor involves both lobes
T3 Palpable tumor extending through prostate capsule and/or seminal vesicle(s)
T3a Unilateral extracapsular extension
T3b Bilateral extracapsular extension
T3c Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than the seminal vesicles
T4a Tumor invades bladder neck and/or external sphincter and/or rectum
T4b Tumor invades other areas near prostate

TNM Classification System (N)

N+ Involvement of regional lymph nodes (LN)
NX Regional LN cannot be assessed
N0 No regional LN metastases
N1 Cancer has spread to 1 LN, (<2 cm)
N2 Cancer has spread to 1 or more LN, (2-5 cm)
N3 Cancer has spread to at least 1 LN, (>5 cm)

TNM Classification System (M)

M+ Distant metastatic spread
MX Presence of distant metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Involvement of non regional lymph nodes
M1b Involvement of bone(s)
M1c Involvement of other distant sites

Carter BH, Partin AW. Campbell's Urology 8th Ed. Philadelphia Pa. WB Saunders; 2002:3065

APPENDIX 2: Drugs not permitted by the study protocol:

Anabolic steroids
Barbiturates
Betamethasone (unless patient has been stable on this drug for more than 3 months)
Bicalutamide
Carbamazepine (unless patient has been stable on this drug for more than 3 months)
Chlorpromazine (unless patient has been stable on this drug for more than 3 months)
Cimetidine
Clomiphene
Cyproterone Acetate (except when given as anti-flare medication with the first injection)
Deflazacort
Dexamethasone (unless patient has been stable on this drug for more than 3 months)
Diethylstilboestrol
Digoxin (unless patient has been stable on this drug for more than 3 months)
Dutasteride
Finasteride
Fluphenazine
Flutamide
Gabapentin (unless patient has been stable on this drug for more than 3 months)
Gonadorelin
Gonadotropin
Goserelin
Hydrocortisone (unless patient has been stable on this drug for more than 3 months)
Ketoconazole (topical use is allowed)
Lamotrigine
Leuprorelin
Levetiracetam
Mesterolone
Methotripmeprazine
Methylprednisolone
Metoprolol
Metyrapone
Pericyazine
Perphenazine
Phenobarbital
Phenytoin (unless patient has been stable on this drug for more than 3 months)
Pipotiazine
Prochlorperazine (unless patient has been stable on this drug for more than 3 months)
Promazine
Sodium Valproate (unless patient has been stable on this drug for more than 3 months)
Spironolactone
Testosterone
Tetracycline
Thioridazine
Tiagabine
Topiramate
Trifluoperazine
Vigabatrin

APPENDIX 3: SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTCS: DECAPEPTYL SR 3MG

1. NAME OF THE MEDICINAL PRODUCT

DECAPEPTYL SR 3mg, powder for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Triptorelin (I.N.N.) 4.2 mg, as triptorelin acetate.
The vial contains an overage to ensure that a dose of 3mg is administered to the patient.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for injection, sustained release formulation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration (see section 5.1).
Treatment of metastatic prostate cancer.
Treatment of endometriosis.
Treatment of uterine fibroids prior to surgery or when surgery is not appropriate

4.2 Posology and method of administration

Prostate cancer
One intramuscular injection should be administered every 4 weeks (28 days). No dosage adjustment is necessary in the elderly.

Endometriosis and uterine fibroids
One intramuscular injection every 28 days. For the treatment of endometriosis and uterine fibroids the treatment must be initiated in the first five days of the cycle. The maximum duration of treatment should be 6 months. For patients with uterine fibroids DECAPEPTYL SR 3mg should be administered for a minimum of 3 months.

A second course of treatment by DECAPEPTYL SR 3mg or by other GnRH analogues should not be undertaken due to concerns about bone density losses.

4.3 Contraindications

Hypersensitivity of GnRH analogues or to any of the excipients.
In prostate cancer, DECAPEPTYL SR 3mg should not be prescribed in patients presenting with spinal cord compression or evidence of spinal metastases.
In endometriosis and uterine fibroid treatment, confirm that the patient is not pregnant before beginning treatment.

4.4 Special warnings and precautions for use

Prostate cancer
Initially, DECAPEPTYL 3mg causes a transient increase in serum testosterone and consequent worsening of symptoms including increase in bone pain (and acid phosphatase levels). Consideration should be given to the use of an anti-androgen for three days prior to DECAPEPTYL SR 3mg treatment, to counteract this initial rise in serum testosterone levels. During the first month of treatment, patients presenting with, or at particular risk of developing, ureteric obstruction should be carefully monitored, as should those at risk of developing spinal cord compression. Continued treatment with DECAPEPTYL SR 3mg leads to suppression of testosterone (and dihydrotestosterone) and consequent improvement in the disease.

Endometriosis and uterine fibroids
Regular administration, every 28 days of one vial of DECAPEPTYL SR 3mg causes a persistent hypogonadotrophic amenorrhoea. During the first month of treatment, a non-hormonal contraception should be given. A supervening metrorrhagia in the course of treatment, other than in the first month, should lead to measurement of plasma oestradiol levels. Should this level be less than 50 pg/mL, possible associated organic lesions should be sought. After withdrawal of treatment, ovarian function resumes and ovulation occurs on average 58 days after the last injection, with first menses occurring on average 70 days after the last injection. Contraception may therefore be required. Due to concerns about bone density losses, DECAPEPTYL SR 3mg should be used with caution in women with known metabolic bone disease.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of LHRH receptors in the pituitary.

4.6 Pregnancy and lactation

Reproductive studies in primates have shown no maternal toxicity or embryotoxicity, and there was no effect on parturition. Inadvertent administration of triptorelin during human pregnancy has not demonstrated a teratogenic or other foetal risk. However, it is recommended that DECAPEPTYL SR 3mg should not be used during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

There is no evidence that DECAPEPTYL SR 3mg has any effect on the ability to drive or operate machinery.

4.8 Undesirable effects

Prostate cancer
In prostate cancer patients, the most frequent side-effects of hot flushes, decreased libido, and impotence are a result of the decrease in testosterone levels. Bone pain, as a result of "disease flare", occurs occasionally. Pain and erythema at injection site, phlebitis and moderate and transient hypertension have been reported. On rare occasions the following have been reported: gynaecomastia, gastralgia, dry mouth, headaches, recurrence of asthma, increased dysuria, fever, pruritus, sweating, paresthesias, dizziness, insomnia, excessive salivation, gastric disturbance, nausea, vertigo, slight hair loss, induration at injection site**.**

Endometriosis and uterine fibroid patients
In endometriosis and uterine fibroid patients, adverse effects such as hot flushes, menorrhagia and vaginal dryness, reflect the efficacy of pituitary-ovarian blockade. Cutaneous rash, hair loss, asthenia, headache, weight gain, oedema, arthralgia, myalgia, transient sight disturbances and temporary hypertension may occur. As with any GnRH analogue, a small loss in bone density, specifically trabecular bone density, occurs during six months of DECAPEPTYL SR 3mg treatment. Clinical data suggests that this loss is reversible.

In the studies of uterine fibroids, surgical intervention as a result of an increase in vaginal haemorrhage was a rare complication of GnRH therapy.
With uterine fibroid patients it is important to monitor the early response to GnRH analogues and if there is no change or even an increase in uterine volume then the possibility of uterine leiomyosarcoma should be considered.

4.9 Overdose

There is no human experience of overdosage. Animal data do not predict any effects other than those on sex hormone concentration and consequent effect on the reproductive tract. If overdosage occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin-Releaseing Hormone analogue

L 02 A E 04: Antineoplastic and immunomodulator

Triptorelin is a decapeptide analogue of GnRH which initially stimulates release of pituitary gonadotrophins.

Prostate cancer patients
This results in an increase in peripheral circulating levels of testosterone and dihydrotestosterone. Continued administration (over 7 days) however, leads to suppression of gonadotrophins and a consequent fall in plasma testosterone. In prostate cancer patients, plasma testosterone levels fall to castrate levels after 2-3 weeks of treatment, frequently resulting in an improvement of function and objective symptoms.
The efficacy and safety of triptorelin has been determined in clinical studies involving 645 patients with locally advanced or metastatic prostate cancer.
Of these, three long term controlled studies compared the efficacy and safety of triptorelin to bilateral orchidectomy as an initial therapy in patients with locally advanced or metastatic prostate cancer (stage C or D). In one of these three long term studies, 7 patients in the triptorelin group and 7 patients in the orchidectomy group had also undergone prostatectomy. Triptorelin induced biochemical castration at least as rapidly as surgical pulpectomy and was as effective as surgical castration in the long term palliative treatment of locally advanced or metastatic prostate cancer. Both the triptorelin and orchidectomy groups showed improvements in dysuria and pain, and reduction in volume of prostate. Analysis after six and eight years in two of the studies showed that there was no significant difference in the median survival rates in the triptorelin group versus the orchidectomy group.
A study assessing the pharmacodynamic equivalence between triptorelin 3-month and 28-day prolonged release formulations in patients with locally advanced or metastatic prostate cancer, found that equivalent testosterone suppression was achieved, whether 3 doses of Decapeptyl SR 3mg (n=68) or a single dose of Decapeptyl SR 11.25mg (n=63) was given. The percentage of patients who achieved a testosterone castrate level $\leq$ 0.5 ng/mL at D84 was similar in the two treatment groups (98% and 96% in the 3-month and 28-day formulation groups, respectively). The time to achieve chemical castration was not significantly different between the two groups.

Endometriosis and uterine fibroid patients
Continued administration of DECAPEPTYL SR 3mg induces suppression of oestrogen secretion and thus enables resting of ectopic endometrial tissue. In pre-operative therapy for uterine fibroids there appears to be a beneficial effect on the blood loss at surgery. Studies have demonstrated a consistent and marked reduction in uterine and/or fibroid volume becoming maximal in a three to six month treatment period. Clinical studies have shown that 90-100% of fibroid patients become amenorrhoeic within two months of treatment and triptorelin provides relief from the symptoms of abdominal pain, dysmenorrhoea and menorrhagia associated with uterine fibroids.

5.2 Pharmacokinetic properties

SUBCUTANEOUS FORM

In healthy volunteers:
Subcutaneously administered triptorelin (100 μg) is rapidly absorbed (Tmax = 0.63 ± 0.26 hr for peak plasma concentration = 1.85 ± 0.23 ng/ml). Elimination is effected with a biological half-life of 7.6 ± 1.6 hr, after a 3 to 4 hr distribution phase. Total plasma clearance is : 161 ± 28 ml/min. Distribution volume is 104.1 ± 11.7 litres.

In prostate cancer patients:
With subcutaneous administration (100 μg), triptorelin blood levels oscillate between maximum values of 1.28 ± 0.24 ng/ml (Cmax) obtained in general one hour after injection (Tmax) and minimum values of 0.28 ± 0.15 ng/ml (Cmin) obtained 24 hrs after injection.
The biological half-life is on average 11.7 ± 3.4 hr but varies according to patients. Plasma clearance (118 ± 32 ml/min) reflects slower elimination in patients, whilst distribution volumes are close to those of healthy volunteers (113.4 ± 21.6 litres).

SUSTAINED RELEASE FORM

Prostate cancer patients
Following intramuscular injection of the sustained release form, an initial phase of release of the active principle present on the surface of the microspheres is observed, followed by further fairly regular release (Cmax = 0.32 ± 0.12 ng/ml), with a mean rate of release of triptorelin of 46.6 ± 7.1 μg/day. The bioavailability of the microparticles is approximately 53% at one month.

Endometriosis and uterine fibroid patients
After intramuscular injection of DECAPEPTYL SR 3mg in endometriosis and uterine fibroid patients the maximum blood level of triptorelin is obtained between 2 to 6 hours after injection, the peak value reached is 11 ng/ml. There was no evidence of accumulation of the product following monthly injections over six months. The minimum blood level oscillates between 0.1 and 0.2 ng/ml. The bioavailability of the sustained release product is approximately 50%.

5.3 Preclinical safety data

Preclinical findings were only those related to the expected pharmacological activity of triptorelin, namely down-regulation of the hypothalamic-pituitary-gonadal axis. These included atrophy of the testes and genital tract, with resultant suppression of spermatogenesis, together with decreased weight of the prostate gland. These findings were largely reversible within the recovery period. In a small number of rats, in a 24 months oncogenicity study, a low incidence of benign histological changes were seen in the non-glandular part of the fore stomach. Erosions, ulcers, necrosis and inflammation were seen at varying degrees of severity. The clinical relevance of these findings is unknown. The increased incidence of adenomatous tumours in the rat pituitary observed with DECAPEPTYL following long-term repeated dosing is thought to be a class specific action of GnRH analogues due to an hormonally-mediated mechanism and has not been found in the mouse nor has it been described in man.
Standard mutagenicity testing revealed no mutagenic activity of triptorelin

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D,L-lactide/glycolide copolymer
Mannitol
Carmellose sodium
Polysorbate 80

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

18 months.
The product should be used immediately after reconstitution

6.4 Special precautions for storage

Do not store above 25°C. Keep the container in the outer carton

6.5 Nature and contents of container

A type I, 5ml capacity glass vial with an elastomer stopper and an aluminium cap containing the powder.
Type I, 3ml capacity glass ampoule containing 2ml of the suspension vehicle.
One syringe and two needles.

6.6 Special precautions for disposal and other handling

The suspension for injection must be reconstituted following the aseptic technique and using exclusively the provided ampoule of mannitol solution 0.8% for injection, suspension vehicle for DECAPEPTYL SR 3mg.
The vehicle should be drawn into the syringe provided using the pink needle and transferred to the vial containing the powder for injection. The vial should be gently shaken and the mixture then drawn back into the syringe without inverting the vial. The needle should then be changed and the green needle used to administer the injection immediately.

7. MARKETING AUTHORISATION HOLDER

Ipsen Limited
190 Bath Road
Slough
Berkshire
SL1 3XE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 06958/0017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 January 2002

10. DATE OF REVISION OF THE TEXT

February 2007

SUMMARY OF PRODUCT CHARACTERISTICS: DECAPEPTYL SR 11.25MG

1. NAME OF THE MEDICINAL PRODUCT

DECAPEPTYL SR 11.25 mg, powder for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Triptorelin (I.N.N.) 15 mg, as triptorelin acetate.
The vial contains an overage to ensure that a dose of 11.25 mg is administered to the patient.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for injection, sustained release formulation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration (see section 5.1).
Treatment of metastatic prostate cancer.
Treatment of endometriosis.
Treatment of precocious puberty (onset before 8 years in girls and 9 years in boys).

4.2 Posology and method of administration

Prostate cancer
One intramuscular injection should be administered every 3 months.
No dosage adjustment is necessary in the elderly.

Endometriosis
One intramuscular injection should be administered every 3 months. The treatment must be initiated in the first five days of the menstrual cycle. Treatment duration depends on the initial severity of the endometriosis and the changes observed in the clinical features (functional and anatomical) during treatment. The maximum duration of treatment should be 6 months (two injections).
A second course of treatment with DECAPEPTYL SR 11.25 mg or with other GnRH analogues should not be undertaken due to concerns about bone density losses.

Precocious puberty
One intramuscular injection of Decapeptyl *SR* 11.25mg repeated every 3 months.
Treatment should be stopped around the physiological age of puberty in boys and girls and should not be continued in girls with a bone maturation of more than 12 years. There are limited data available in boys relating to the optimum time to stop treatment based on bone age, however it is advised that treatment is stopped in boys with a bone maturation age of 13-14 years.

Contraindications

Hypersensitivity of GnRH analogues or to any of the excipients.
In prostate cancer, DECAPEPTYL SR 11.25 mg is contraindicated in patients presenting with spinal cord compression or evidence of spinal metastases.
In endometriosis, confirm that the patient is not pregnant before beginning treatment.

4.4 Special warnings and precautions for use

In adults the prolonged use of GnRH analogues may lead to bone loss which enhances the risk of osteoporosis.

Prostate cancer
Initially, DECAPEPTYL SR 11.25 mg like other GnRH analogues causes a transient increase in serum testosterone and consequent worsening of symptoms including increase in bone pain (and serum acid phosphatase levels). Continued treatment with DECAPEPTYL SR 11.25 mg leads to suppression of testosterone (and dihydrotestosterone) and consequent improvement in the disease. During the first month of treatment, patients presenting with, or at particular risk of developing, urinary tract obstruction should be carefully monitored, as should those at risk of developing spinal cord compression. Consideration should be given to the use of an anti-androgen for three days prior to DECAPEPTYL SR 11.25 mg treatment, to counteract this initial rise in serum testosterone levels.

Endometriosis
At the recommended dose, DECAPEPTYL SR 11.25 mg causes a persistent hypogonadotrophic amenorrhoea. A supervening metrorrhagia in the course of treatment, other than in the first month, should lead to measurement of plasma oestradiol levels. Should this level be less than 50 pg/mL, possible associated organic lesions should be sought**.** After withdrawal of treatment, ovarian function resumes, with ovulation expected to occur approximately 5 months after the last injection**.** A non-hormonal method of contraception should be used throughout treatment including for 3 months after the last injection.
Due to concerns about bone density losses, DECAPEPTYL SR 11.25 mg should be used with caution in women with known metabolic bone disease.

Precocious puberty (in girls)
Initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen withdrawal, may lead, in the first month, to vaginal bleeding of mild or moderate intensity.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of LHRH receptors in the pituitary.

4.6 Pregnancy and lactation

Animal studies have not revealed any teratogenic effects. During post-marketing surveillance and in a limited number of pregnant women who were exposed inadvertently to triptorelin, there were no reports of malformation or foetotoxicity attributable to the product. However, as the number of patients is too small to draw conclusions regarding the risk of foetal malformations or foetotoxicity, if a patient becomes pregnant while receiving triptorelin, therapy should be discontinued.
Triptorelin is not recommended for use during lactation.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Prostate cancer
The most frequently occurring side-effects of treatment with triptorelin are hot flushes, decreased libido and impotence, each reported by> 10 % of patients in clinical trials using DECAPEPTYL SR 11.25 mg.
At the beginning of treatment increased bone pain, worsening of genito-urinary obstruction symptoms (haematuria, urinary disorders) and/or worsening of neurological signs of vertebral

metastases (back pain, weakness or paresthesia of the lower limbs) are commonly observed, resulting from the initial and transient increase in plasma testosterone. These symptoms disappear in one or two weeks.
The following uncommon adverse reactions have been observed during clinical trials with other triptorelin formulations: hypertension, gynaecomastia, insomnia, mood disorders, emergence of psychiatric disorders, vertigo, dizziness.
Additional rare adverse reactions reported among patients treated with other marketed triptorelin formulations are: allergic reactions (rash, pruritus, urticaria, and very occasionally Quincke's oedema), phlebitis, dry mouth or excessive salivation, headaches, recurrence of asthma, fever, sweating, weight increase, pain/erythema/induration at injection site, gastralgia, gastric disturbance, nausea, vomiting, slight hair loss, visual disturbances.

Endometriosis
At the beginning of treatment the symptoms of endometriosis (pelvic pain, dysmenorrhoea) may be exacerbated during the initial and transient increase in plasma oestradiol levels. These symptoms should disappear in one or two weeks. Genital haemorrhage including menorrhagia, metrorrhagia or spotting may occur in the month following the first injection.
During clinical trials the adverse reactions showed a general pattern of hypo-oestrogenic events related to pituitary-ovarian blockade such as hot flushes, sweating, sleep disturbances, headache, mood changes, vaginal dryness, dyspareunia, and decreased libido.
Transient pain, redness or local inflammation at the injection site may occur.
The following adverse reactions have been observed during clinical trials with other triptorelin formulations: breast pain, muscle cramps, joint pain, weight gain, nausea, abdominal pain or discomfort, asthenia, increased blood pressure, episodes of blurred or abnormal vision, cutaneous rash, oedema, hair loss.
As with any GnRH analogue, a small loss in bone density, specifically trabecular bone density, occurs during six months of DECAPEPTYL SR 11.25 mg treatment. Clinical data suggests that this loss is reversible.

Precocious Puberty
Mild or moderate withdrawal bleeding (common) may occur in girls in the first month of treatment.
Additional common adverse reactions may be observed such as injection site reactions and arthralgia.
According to the cumulative safety experience with triptorelin in children treated for precocious puberty, in addition the following rare reactions have been reported from post-marketing surveillance: allergic reactions, headache, weight gain, increased blood pressure, episodes of blurred or abnormal vision, gastrointestinal tract discomfort with abdominal pain and vomiting, epistaxis, malaise, myalgia, emotional liability, nervousness.

4.9 Overdose

No case of overdose has been reported. Animal data do not predict any effects other than those on sex hormone concentration and consequent effect on the reproductive tract. If overdose occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Gonadotrophin-Releasing Hormone analogue

L 02 A E 04: Antineoplastic and immunomodulator

Triptorelin is a synthetic decapeptide analogue of natural GnRH.

Prostate cancer
The first administration of DECAPEPTYL SR 11.25 mg stimulates the release of pituitary gonadotrophins with a transient increase in testosterone levels (“flare-up”) in men and in oestradiol levels in women. Prolonged administration leads to a suppression of gonadotrophins and a fall in plasma testosterone or oestradiol to castrate levels after approximately 20 days, which is maintained for as long as the product is administered.
The efficacy and safety of triptorelin has been determined in clinical studies involving 645 patients with locally advanced or metastatic prostate cancer.
Of these, three long term controlled studies compared the efficacy and safety of triptorelin to bilateral orchidectomy as an initial therapy in patients with locally advanced or metastatic prostate cancer (stage C or D). In one of these three long term studies, 7 patients in the triptorelin group and 7 patients in the orchidectomy group had also undergone prostatectomy. Triptorelin induced biochemical castration at least as rapidly as surgical pulpectomy and was as effective as surgical castration in the long term palliative treatment of locally advanced or metastatic prostate cancer. Both the triptorelin and orchidectomy groups showed improvements in dysuria and pain, and reduction in volume of prostate. Analysis after six and eight years in two of the studies showed that there was no significant difference in the median survival rates in the triptorelin group versus the orchidectomy group.
A study assessing the pharmacodynamic equivalence between triptorelin 3-month and 28-day prolonged release formulations in patients with locally advanced or metastatic prostate cancer, found that equivalent testosterone suppression was achieved, whether 3 doses of Decapeptyl SR 3mg (n=68) or a single dose of Decapeptyl SR 11.25mg (n=63) was given. The percentage of patients who achieved a testosterone castrate level $\leq$ 0.5 ng/mL at D84 was similar in the two treatment groups (98% and 96% in the 3-month and 28-day formulation groups, respectively). The time to achieve chemical castration was not significantly different between the two groups.

Endometriosis
The first administration of DECAPEPTYL SR 11.25 mg stimulates the release of pituitary gonadotrophins with a transient increase in testosterone levels (“flare-up”) in men and in oestradiol levels in women. Prolonged administration leads to a suppression of gonadotrophins and a fall in plasma testosterone or oestradiol to castrate levels after approximately 20 days, which is maintained for as long as the product is administered.
Continued administration of DECAPEPTYL SR 11.25 mg induces suppression of oestrogen secretion and thus enables resting of ectopic endometrial tissue.

Precocious Puberty
Inhibition of the increased hypophyseal gonadotropic activity in children with precocious puberty leads to suppression of oestradiol and testosterone secretion in girls and boys, respectively, and to lowering of the LH peak due to the LHRH stimulation test. The consequence is a regression or stabilisation of secondary sex characteristics and an improvement in median predicted adult height of 2.3cm after one year's treatment.

5.2 Pharmacokinetic properties

Following intramuscular injection of DECAPEPTYL SR 11.25 mg in patients (men and women), a peak of plasma triptorelin is observed in the first 3 hours after injection. After a phase of decrease, the circulating triptorelin levels remain stable at around 0.04-0.05ng/ml in endometriosis patients and around 0.1ng/ml in prostate cancer patients until day 90.

5.3 Preclinical safety data

The compound did not demonstrate any specific toxicity in animal toxicological studies. The effects observed are related to the pharmacological properties of triptorelin on the endocrine system.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D,L lactide-glycolide copolymer
Mannitol
Carmellose sodium
Polysorbate 80.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except the one mentioned in 6.6.

6.3 Shelf life

2 years.
The product should be used immediately after reconstitution.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

A type I, 4 ml capacity glass vial with an elastomer stopper and an aluminium cap containing the powder.
A type I, 3 ml capacity glass ampoule containing 2 ml of the suspension vehicle.
One syringe and 2 needles.

6.6 Special precautions for disposal and other handling

The suspension for injection must be reconstituted following the aseptic technique and using exclusively the provided ampoule of mannitol solution 0.8% for injection, suspension vehicle for DECAPEPTYL SR 11.25 mg.
The suspension vehicle should be drawn into the syringe provided using the pink needle and transferred to the vial containing the powder for injection. The vial should be gently shaken and the mixture then drawn back into the syringe without inverting the vial. The needle should then be changed and the green needle used to administer the injection immediately. The vial is intended for single use only and any remaining product should be discarded.

7. MARKETING AUTHORISATION HOLDER

Ipsen Limited
190 Bath Road
Slough
Berkshire
SL1 3XE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

06958/0016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 October 2002

10. DATE OF REVISION OF THE TEXT

February 2007

APPENDIX 4: UHB ADVERSE EVENTS FORMS

UHB Investigator's Template for recording Adverse Events

Full title of Study: A Phase II, Open-Label, Single-Arm Study To Assess The Efficacy And Safety Of Decapeptyl® Sr (3 mg And 11.25 mg formulations) When Administered By Subcutaneous Injection			
Ethics No:		UHB Project Registration no:	SU/2006/2424

Sheet number : _____ of _____

AE No:	Patient ID	Description of Event	Start date	Duration/End date	Outcome
					☐ Resolved ☐ Ongoing ☐ Ongoing with sequelae**

**Sequelae

Assessment			
Intensity:	☐ mild ☐ moderate ☐ severe	Expectedness	☐ expected ☐ unexpected i.e. not described in protocol, product information or investigator brochure.
Causality: Relationship to study drug/device/intervention	☐ not related ☐ unlikely to be related ☐ possibly related ☐ probably related ☐ definitely related	Seriousness	☐ Not serious ☐ Results in death* ☐ Life threatening* ☐ Results in hospitalisation or prolongation of existing hospitalisation* ☐ Results in disability or incapacity* ☐ Congenital anomaly or birth defect* ☐ Other (please specify)*
Was the patient withdrawn from the study as a result of the AE ☐ Yes ☐ No			Did the patient receive treatment for the AE? ☐ No ☐ Yes (If yes please describe)

* Event is considered serious – report to the sponsor: UHB R&E department within 24 hours using the UHB SAE form provided.

Signature of person completing form: _____ Date:_____

R&E Use Only: Case Reference Number		Date report received by R&E	

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM (page 1 of 4)

1. Person making report	
Name:	
Job Title/Role In Study:	
Contact address:	
Email address:	
Telephone No:	
Fax number:	

2. Details of study	
Full Title of Study: A Phase II, Open-Label, Single-Arm Study to Assess the Efficacy and Safety of Decapeptyl® SR (3 mg and 11.25 mg formulations) when administered by subcutaneous injection.	Study site (e.g. Hospital name): UHB R&D Project Registration No: SU/2006/2424 Ethics No: EudraCT No (IMP studies only): 2006-006595-38

3. Details of subject affected by SAE/SUSAR						
Subject study ID	Hospital Number	Initials	DoB	Gender	Weight	Height

4. Details of SAE/SUSAR (further space available in section 12)

Full description of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:

Event is defined as serious because it (tick as many as apply):	*Specify:
☐ resulted in death ☐ is/was life-threatening ☐ resulted in persistent or significant disability/incapacity ☐ required hospitalisation ☐ prolonged an ongoing hospitalisation ☐ resulted in a congenital anomaly or birth defect ☐ other – please specify* Please give further details in section 6 'Outcome'	

Maximum intensity (up until time of initial report)	Mild ☐	Moderate ☐	Severe ☐

Onset Date (when event became serious)	Onset Time	End date	End time	*OR* Duration

Signature of person making report: _____Date:____/____/_____

R&E use only: case reference number	

To be completed by the person filling in the SAE form					
UHB R&D no.:	SU/2006/2424	*Subject ID/initials*		*Onset date of SAE*	

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM (page 2 of 4)

5. Details of IMP/device/intervention(s) if applicable (further space available in section 12)			
Name of drug/device/intervention	Total daily dose (if applicable)	Dosing regime (inc route)	Date/time of last dose/intervention

6. Outcome (further space available in section 12)		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
*Give details:		
Was the patient withdrawn from the study?	Yes ☐	No ☐

7. Location of (onset of) SAE (further space available in section 12)
Setting (e.g. hospital*, home, GP, nursing home):
*If SAE occurred on UHB precinct give exact location:

8. Action taken and further information (further space available in section 12)
Please describe action taken:
Other information relevant to assessment of case e.g. medical history, family history, test results.

Signature of person making report: _____**Date:**____**/**____**/**____

R&E use only: case reference number	

To be completed by the person filling in the SAE form					
UHB R&D no.:	SU/2006/2424	*Subject ID/initials*		*Onset date of SAE*	

RESEARCH RELATED SAE/SUSAR <u>INITIAL</u> REPORT FORM (page 3 of 4)

9. Causality and Expectedness (to be completed by physician)		
Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related ☐ Possibly related* ☐ Probably related* ☐ Definitely related*	***If possibly, probably or definitely related, was the SAE unexpected? ☐ Yes[1] ☐ No[2] (Unexpected means not described in the protocol or other product information)	***In addition to this form, and within 5 days:*** **1 - Please complete and return all sections of the follow up report form.** **2 - Please complete and return sections 1, 2 and 3 of the follow up report form.**
For blinded studies: Has the randomisation code been broken in making this assessment: ☐ Yes* ☐ No *If yes, give details of randomisation:		
10. Sponsor notification (only complete where sponsor is not UHB)		
Has the Sponsor been notified of the SAE/SUSAR?	☐ Yes, give date: ☐ No+	
+***Please note, you must inform the Sponsor within 24 hours of becoming aware of the event.***		
11. Chief/Principal Investigator, or delegated physician (at this site)		
Name:		
Job title/role in study:		
Contact address:		
Email address:		
Telephone No:		
Fax number:		
Signature: I confirm that the contents of this form (pages 1, 2, 3 ± 4) are accurate and complete		

Please tick this box if section 12 (next page) has been used: ☐

Signature of person making report: _____Date:____/____/____

R&E use only: case reference number		Date received	

To be completed by the person filling in the SAE form					
UHB R&E no.:	SU/2006/2424	*Subject ID/initials*		*Onset date of SAE*	

RESEARCH RELATED SAE/SUSAR <u>INITIAL</u> REPORT FORM (page 4 of 4)

12. Additional information (refer to section number)	
Section No.	Further information

Signature of person making report: _____Date:____/____/____

R&E use only: case reference number		Date received	

To be completed by the person filling in the SAE form					
UHB R&D no.:	SU/2006/2424	*Subject ID/initials*		*Onset date of SAE*	

RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM (Page 1 of 3)

1. Further details of SAE/SUSAR			
Further details of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:			
Maximum intensity (up until time of follow up report)	Mild ☐	Moderate ☐	Severe ☐
	End date	End time	*OR* Duration

2. Outcome		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
*Give details:		

Was the patient withdrawn from the study?	Yes ☐	No ☐

3. Additional action taken and further information since initial report
Please describe further action taken:
Further information or missing data relevant to assessment of case e.g. medical history, family history, test results.

Signature of person making report:_____Date:____/____/____

Name (please print):_____ Job title:_____

Signature of chief /principal investigator or delegated physician:
Name (print please):
I confirm that the contents of this form (pages 1± 2/3) are accurate and complete

R&E use only: case reference number	

To be completed by the person filling in the SAE form					
UHB R&D number:	SU/2006/2424	*Subject ID/initials*		*Onset date of SAE*	

RESEARCH RELATED SAE/SUSAR <u>FOLLOW UP</u> REPORT FORM (page 2 of 3)

Sheet number: _____of _____

4. CONCOMITANT MEDICATION – details of administration of other medication concurrent with the IMP(s)/device/intervention.								
Brand name:	Indication	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	*Or* duration of treatment

<u>Continue on new sheet if necessary; please identify how many sheets have been used.</u>

Signature of person making report:_____**Date:**_____**/**_____**/**_____

R&E use only: case reference number	

To be completed by the person filling in the SAE form					
UHB R&D number:	SU/2006/2424	*Subject ID/initials*		*Onset date of SAE*	

RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM (Page 3 of 3)

Sheet number: _____of _____

5. STUDY IMP – details of administration. **NB complete for IMP studies only**

Brand name:	Indication	Batch no.	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	*Or* duration of treatment

For blinded studies, was the randomisation code broken?	☐	*Yes	☐	No

*If yes, give details:

Continue on new sheet if necessary; please identify how many sheets have been used.

Name of person completing report: _____

Signature of person making report:_____**Date:**_____/_____/_____