New Medicine Assessment

TRIPTORELIN

Recommendation: Amber 0 for the following indications:

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

Summary of supporting evidence:

- Gonadotrophin hormone releasing hormone agonists (GnRHa) are the only effective treatment for central precocious puberty (CPP).
- All available GnRHa are effective despite different routes of administration, dosing, and duration of action.
- Decades of experience have shown that GnRHa treatment is both safe and effective.
- The longer acting sustained release GnRHa preparations are a similar annual cost to the shorter acting version and may improve compliance.
- Triptorelin is established treatment for this indication. It has been recommended for use in Scotland since 2005.
- Triptorelin is one of only two licensed drugs in the UK for this indication.
- Treatment with GnRH agonists should always be initiated and monitored by a specialist (Consultant Paediatric Endocrinologist or Consultant Paediatrician with expertise in growth disorders).
- It is the specialist/consultant's responsibility to monitor a patient's growth, pubertal development, assessment of any other ongoing or evolving endocrinopathy and general condition at 3-6 monthly intervals following instigation of therapy and advise about change in dose, preparation or frequency of injections. Also to supervise the timing of cessation of therapy based on patient's gender, age and other medical problems.
- There is a risk of idiopathic intracranial hypertension with gonadotropin releasing hormone (GnRH) analogues.
- Information with regards to future fertility is still limited.
- Allergic and anaphylactic reactions have been reported in adults and children.

Details of Review

Name of medicine (generic & brand name)**:**

Triptorelin

Strength(s) and form(s):

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

Decapeptyl SR 22.5 mg (triptorelin pamoate), powder and solvent for suspension for injection

Decapeptyl SR 3 mg (triptorelin acetate), powder and solvent for suspension for injection

Gonapeptyl depot 3.75 mg (triptorelin acetate), powder and solvent for suspension for injection

Salvacyl 11.25 mg (triptorelin embonate), powder and solvent for prolonged-release suspension for injection

Dose and administration:

The treatment of children with triptorelin should be under the overall supervision of a paediatric endocrinologist or of a paediatrician or endocrinologist with expertise in the treatment of central precocious puberty. Products licensed for precocious puberty:

Decapeptyl SR 11.25 mg (triptorelin pamoate)[1]

Central precocious puberty (before 8 years in girls and 10 years in boys).

One intramuscular injection should be administered 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 to 13 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.

Decapeptyl SR 22.5 mg (triptorelin pamoate)[2]

Central precocious puberty (before 8 years in girls and 10 years in boys)

Administer every six months (twenty four weeks) as a single intramuscular injection.

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 12-13 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.

Gonapeptyl depot 3.75 mg (triptorelin acetate)[3]

Dosing at the beginning of treatment should be based on body weight, one injection of triptorelin should be injected on days 0, 14, and 28. Thereafter one injection every 4 weeks. Should the effect be insufficient, the injections may be given every 3 weeks. Dosing should be based on body weight according to the table.

Body weight	Dosing
‹ 20 kg	1.875 mg (half dose)
20 – 30 kg	2.5 mg (2/3 dose)
› 30 kg	3.75 mg (full dose)

Treatment should be stopped if a bone maturation of older than 12 years in girls and older than 13 years in boys has been achieved.

BNF therapeutic class / mode of action:[4]

Gonadotrophin-releasing hormones –

Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

Inhibition of the increased hypophyseal gonadotropic activity in children with central 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 GnRH 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.[1]

Licensed indication(s): *NB. Not all preparations are licensed for all listed indications.*
Treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration.

Treatment of metastatic prostate cancer.

As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

As neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

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

Treatment of endometriosis.

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

Treatment of uterine fibroids prior to surgery or when surgery is not appropriate.

As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as pre-menopausal after completion of chemotherapy.

Preoperative reduction of myoma size to reduce the symptoms of bleeding and pain in women with symptomatic uterine myomas.

Symptomatic endometriosis confirmed by laparoscopy when suppression of the ovarian hormonogenesis is indicated to the extent that surgical therapy is not primarily indicated.

(A preparation of triptorelin embonate marketed as the product Salvacyl is indicated for the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations)

Proposed use (if different from, or in addition to, licensed indication above):

Precocious puberty.

Course and cost:

Treatment length will vary from child to child.

Triptorelin 11.25mg powder and solvent for suspension for injection vial = £207

1 injection every 3 months.

1 year = £828

5 years = £4140

Triptorelin 22.5mg powder and solvent for suspension for injection vials = £414

1 injection every 6 months.

1 year = £828

5 years = £4140

Triptorelin 3.75mg powder and solvent for suspension for injection pre-filled syringes = £82

3 initial doses = £246

Then 3-4 weekly = £1066 - £1394 /year

Drug tariff prices Oct 2023

Current standard of care/comparator therapies:

Gonadotrophin-releasing hormones

Goserelin (Zoladex) [Not licensed in children] Zoladex LA 10.8mg SC every 12 weeks (or more frequently) Zoladex 3.6mg SC every 28 days (or more frequently) Leuprorelin acetate (Prostap) [Licensed in children] Prostap 3 DCS SC every 3 months Prostap SR DCS SC every month
Relevant NICE guidance: None

Background and context

Precocious puberty is commonly defined as puberty that starts before age 8 in girls and 9 in boys. Most cases of precocious puberty in girls are idiopathic and the benefits of early identification and treatment are subject to much debate. Precocious puberty in boys is less common, but proportionally much more likely to have a serious cause.[5]

The diagnosis is based on a combination of the following:[8]

1. Girls: Presence of pubic hair and/or breast development before 8 years
2. Boys: Presence of pubic hair and/or development of genitalia before 9 years
3. Rapid growth rate resulting in tall stature (for age & for parental heights)
4. Advanced skeletal maturation
5. Central cause of precocious puberty confirmed by pituitary function testing and/or cranial imaging.

The gonadorelin stimulation test is used to distinguish between gonadotrophin-dependent (central) precocious puberty and gonadotrophin-independent precocious puberty. Treatment requires specialist management.[6]

Gonadorelin analogues, used in the management of gonadotrophin-dependent precocious puberty, delay development of secondary sexual characteristics and growth velocity.[6]

[It should be noted that triptorelin is listed as a treatment option on the LSCMMG 'Hormone Therapy in Gender Dysphoria Prescribing Information Sheet' for both trans men and for trans women. Treatment in these cases is RAG rated Amber 0.][7]

Summary of evidence

Summary of efficacy data in proposed use:

British Society for Paediatric Endocrinology and Diabetes Shared Care Guidelines: Use of Gonadotrophin Releasing Hormone (GnRH) Agonists – Triptorelin (2022)[8]

Treatment with GnRH agonists should always be initiated and monitored by a specialist (Consultant Paediatric Endocrinologist or Consultant Paediatrician with expertise in growth disorders) as recognised by the British Society for Paediatric Endocrinology and Diabetes (BSPED).

GnRH agonists have a good safety record. Currently, Triptorelin, Prostap SR DCS and Prostap 3 DCS are licensed for use in children with central precocious puberty. Dose adjustments (by altering the frequency of injections) may be required intermittently and should be instigated by the supervising Consultant based on continuing pubertal changes & hormone (LH, FSH & testosterone/17β oestradiol) levels.

It is the specialist/consultants responsibility to monitor patient's growth, pubertal development, assessment of any other ongoing or evolving endocrinopathy and general condition at 3-6 monthly intervals following instigation of therapy and advise about change in dose, preparation or frequency of injections. Also to supervise the timing of cessation of therapy based on patient's gender, age and other medical problems.

It is important to ensure that the injections are given within the recommended time interval and any delay should be avoided. Pubertal suppression action of GnRH agonists may be lost if injections are unduly delayed and increases the incidence of adverse effects. The injection can be brought forward for a few days if required.

British Medical Journal Best Practice (2023)[9]

The main aims of treatment, in the short term, are to prevent progression of secondary sexual characteristics, and of menarche in girls.

Continuous exposure of the GnRH receptor to GnRH suppresses puberty, as it is only the pulsatile exposure that triggers pubertal progression. Synthetic preparations of GnRH agonists are available with a longer half-life than natural GnRH and are used successfully in the treatment of central precocious puberty (CPP). GnRH agonists are the only effective treatment modality for CPP.

GnRH agonists have the paradoxical effect of down-regulating gondadotrophin release when administered in depot form at a high dose. Intranasal preparations have also been used previously, but are now rendered

obsolete by the depot preparations.

Recommended GnRH agonists include leuprorelin, triptorelin, or goserelin depot preparations.

Treatment improves the adult height to a degree with rapidly progressing puberty, based on calculation of a predicted adult height, particularly in younger children (<6 years old). Suppression of puberty with these agents is reversible with few adverse effects.

Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium (2019)[10]

Prospective comparison studies are needed to establish whether there are differences in efficacy among the GnRHa in use today. Clinicians should discuss all of the available options with patients and families, including the expected duration of the therapy, the frequency of administration, and potential short-term and long-term side effects. The sustained release GnRHa preparations are similar in annual cost and may improve compliance.

Consensus statement on the use of gonadotropin-releasing hormone analogs in children (2009)[11]

The efficacy of GnRHa to increase adult height is undisputed only in early onset (girls younger than 6 yr) CPP. Other key areas, such as the psychosocial effects of CPP and their alteration by GnRHa, need further study. Few controlled prospective studies have been performed with GnRHa in children, and many conclusions rely in part on collective expert opinion. The conference did not endorse commonly voiced concerns regarding the use of GnRHa, such as promotion of weight gain or long-term diminution of bone mineral density. Use of GnRHa in conditions other than CPP requires further investigation and cannot be suggested routinely.

All available GnRHa are effective despite different routes of administration, dosing, and duration of action. The depot preparations are preferred because of improved compliance.

Summary of Product Characteristics[2]

In a non-comparative clinical study, 44 children with central precocious puberty (39 girls and 5 boys) were treated with a total of two intramuscular injections of Decapeptyl SR 22.5 mg over 12 months (48 weeks). Suppression of stimulated LH concentrations to prepubertal levels was achieved in 95.5% of subjects by month 3, and in 93.2 % and 97.7% of subjects at months 6 and 12, respectively.

The consequence is a regression or stabilisation of secondary sex characteristics and slowing down of accelerated bone maturation and growth.

In girls, initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen increase, may lead, in the first month, to uterine 'withdrawal' bleeding of mild or moderate intensity.

Scottish Medicines Consortium (2006)[12]

Triptorelin 11.25mg vial for injection (Decapeptyl SR®) is accepted for use in NHS Scotland for the treatment of precocious puberty (onset before 8 years in girls and 9 years in boys).

For patients for whom this drug is appropriate, it is associated with an increased dose interval (3 months vs. 1 month) and reduced costs compared to an existing pre-filled syringe formulation of triptorelin.

Scottish Medicines Consortium (2005)[13]

Triptorelin (Gonapeptyl Depot) is accepted for use within NHS Scotland for the treatment of confirmed central precocious puberty in girls under nine years and boys under ten years.

In 2005 this was the only licensed medicine for central precocious puberty.

In three open-label uncontrolled trials the licensed dose of triptorelin depot injection was administered to girls and boys aged less than 8 and 9 years, respectively, who had been diagnosed with central precocious puberty. In all trials serum gonadotrophin levels decreased from baseline and puberty stopped or regressed in most patients.

Triptorelin has been compared directly with buserelin intranasal spray and indirectly with buserelin subcutaneous injection. Neither formulation is licensed in the UK for treatment of central precocious puberty. The mean final height of patients in the active treatment groups were greater than in the control group: 153cm and 161cm vs. 150cm, respectively, with the differences between the triptorelin group and each of the other two groups significant.

In uncontrolled trials triptorelin demonstrated efficacy in suppressing pubertal development in children with central precocious puberty. In practice, this is undertaken with the aim(s) of preventing psychological problems and/or improving auxological outcomes. Efficacy data for triptorelin compared to no treatment with respect to these outcomes are limited and available data do not allow the groups of children who benefit from triptorelin to be clearly defined.

Summary of safety data:

US Food and Drug Administration (2021)[14]

Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS):

Idiopathic intracranial hypertension with gonadotropin releasing hormone (GnRH) analogues, such as Triptodur (triptorelin). FDA is evaluating the need for regulatory action.

Evaluation of Hypersensitivity Reactions with Leuprolide Acetate and Triptorelin Acetate in Children (2022)[15]

The aim of this study was to report clinical experience with hypersensitivity reactions seen in paediatric patients receiving leuprolide acetate (LA) and triptorelin acetate (TA) in CPP at the single paediatric tertiary medical centre and to evaluate the incidence rate of hypersensitivity reactions.

Seven adverse reactions (0.69%) were observed among total of 1010 CPP patients who were treated with TA and LA. Sterile abscesses were observed in 3 patients (0.29%). None of the patients had an anaphylaxis. Tremors of both hands, a vomiting episode, an urticarial rash, and musculoskeletal stiffness were observed in one patient each.

Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium (2019)[10]

Adverse effects of GnRHa therapy are rare, and the associations of most reported adverse events with the GnRHa molecule itself are unclear. Decades of experience have shown that GnRHa treatment is both safe and efficacious.

Allergic or local reactions to GnRHa preparations occur rarely and have been inadequately documented. Withdrawal bleeding due to falling oestrogen concentrations may occur after the initiation of GnRHa treatment in girls having a significant endometrial lining. Hot flashes are occasionally seen in the initial phases of GnRHa treatment in girls with CPP. Convulsions have been reported in patients receiving GnRHa in postmarketing reports. A prolonged QT interval associated with GnRHa has not been reported in women or children. This has been reported in adult males treated with GnRHa for prostate cancer. Slipped capital femoral epiphysis has been reported in a small number of patients, occurring during GnRHa treatment or after cessation of GnRHa therapy.

There is no substantiated evidence that GnRHa treatment for CPP impairs reproductive function or reduces fertility. In most girls, gonadal function is restored promptly after cessation of therapy, with subsequent menarche and regular ovulatory menstrual cycles.

Children with CPP often have an elevated bone mineral density (BMD) for their age at diagnosis. GnRHa treatment slows mineral accrual, but after discontinuation BMD appears not to be significantly different from that of their peers by late adolescence.

Scottish Medicines Consortium (2005)[13]

In children adverse-effects associated with triptorelin injection are uncommon and include vaginal bleeding or discharge, gastro-intestinal upset and anaphylaxis. Limited follow-up data were provided and appear to show no adverse effects on bone mineral density, body weight and reproductive function.

Summary of Product Characteristics[1,2,3]

Contraindications

Hypersensitivity to GnRH, its analogues or to any of the excipients.

Pregnancy and lactation.

Special warnings and precautions for use

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists.

In girls, it should be confirmed that the patient is not pregnant before prescribing triptorelin.

Treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.

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.

After discontinuation of treatment the development of puberty characteristics will occur.

Information with regards to future fertility is still limited. In most girls, regular menses will start on average one year after ending the therapy.

Bone mineral density may decrease during GnRH agonist therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped capital femoral epiphysis can be seen after withdrawal of GnRH agonist treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

Allergic and anaphylactic reactions have been reported in adults and children. These include both local site reactions and systemic symptoms.

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving triptorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of triptorelin should be considered.

General tolerance in Children

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to < 1/100); not known; (cannot be estimated from the available data).

Vaginal bleeding may occur in the month following the first injection.

System Organ Class	Very common ≥ 1/10	Common ≥1/100 - <1/10	Uncommon ≥1/1000 - <1/100	Additional post-marketing AEs Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and Nutrition Disorders			Obesity	
Psychiatric disorders			Mood altered	Affect lability Depression Nervousness
Nervous system disorders		Headache		Idiopathic intracranial hypertension (pseudotumor cerebri)
Eye disorders			Visual impairment	Visual disturbance
Vascular disorders		Hot flush		Hypertension

Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders		Abdominal pain	Vomiting Constipation Nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritus Rash Urticaria	Angioneurotic oedema
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation**)**	Malaise	
Investigations		Weight increased		Blood prolactin increased Blood pressure increased

Strengths and limitations of the evidence:

Strengths

- Established treatment.
- Adverse effects of GnRHa therapy are rare.

Limitations

- Prospective comparison studies are needed to establish whether there are differences in efficacy among the GnRHa in use.
- The psychosocial effects of CPP and the effect of GnRHa needs further study.
- Few controlled prospective studies have been performed with GnRHa in children, and many conclusions rely in part on collective expert opinion.

Summary of evidence on cost effectiveness:

Treatment length will vary from child to child.

Drug	Frequency of administration	Unit cost	Drug cost year 1 (approx.)	Drug cost 5 years (approx.)
Triptorelin 11.25mg	**3 monthly**	**£207/vial**	**£828**	**£4140**

Triptorelin 22.5mg	**6 monthly**	**£414/vial**	**£828**	**£4140**
Triptorelin 3.75mg	3 stat, then 3-4 weekly	£82/syringe	£1312 - 1640	£5576 - 7216
Zoladex LA 10.8mg	12 weekly (min)	£235/syringe	£940	£4700
Zoladex 3.6mg	monthly (min)	£70/syringe	£840	£4200
Prostap 3 DCS	3 monthly	£226/syringe	£904	£4520
Prostap SR DCS	monthly	£75/syringe	£900	£4500

Drug tariff prices Oct 2023

Prescribing and risk management issues:

- Conception and contraception - Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.[4]
- Monitor bone mineral density monitoring.[4]

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Triptorelin is one of only 2 licensed drugs for this indication in children.

Financial implications of the intervention:

None identified – costs of comparator therapies are comparable.

Service Impact Issues Identified:

Prescribing may be required in primary care if Amber RAG rating.

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** recommends triptorelin as 'AMBER patient retained by specialist'. There is a prescribing support information sheet for all approved indications.

The **Greater Manchester Medicines Management Group** (GMMMG) recommends triptorelin as Red. Their first choices for precocious puberty are goserelin and leuprorelin.

Examples of the positions in other localities nationally:

Coventry and Warwickshire APC – Shared Care University Hospitals Sussex – Shared Care Leeds - Amber Level 1- Specialist Recommendation Cambridgeshire and Peterborough – Shared Care
Legal Issues Identified:
None identified
Media/ Public Interest:
None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

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[14] US Food and Drug Administration, "July - September 2021 | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS)". Available: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/july-september-2021-potential-signals-serious-risksnew-safety-information-identified-fda-adverse [Accessed 19 October 2023]

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