Berkshire West Integrated Care System
Representing
Berkshire West Clinical Commisioning Group
Royal Berkshire NHS Foundation Trust
Berkshire Healthcare NHS Foundation Trust
Berkshire West Primary Care Alliance

Prescribing Guidelines

Prescribing arrangement for the management of patients transferring from ***Secondary Care to Primary Care***

The use of GnRH Agonists in Central Precocious Puberty (CPP)

APC PG 030

For the latest information on interactions and adverse effects, always consult the latest version of the Summary of Product Characteristics (SPC), which can be found at: http://www.medicines.org.uk/

Approval and Authorisation

Approved by	Job Title	Date
BW CCG Area Prescribing Committee	G Braham, APC Chair	1st May 2019
BW CCG GP MOC	Dr Beecham, GP MOC Chair	22nd May 2019

Change History

Version	Date	Author	Reason
v.1.0		unknown	
v.1.0	October 2017	n/a	Update to APC category
v.1.0	May 2019	A. Scott	Reviewed following expiry

This prescribing guideline remains open to review considering any new evidence.

This guideline should only be viewed online and will no longer be valid if printed off or saved locally

Author	Amaka Scott	Date of production:	Unknown
Job Title	Interface Lead Pharmacist	Review Date	May 2022
Protocol Lead	A Scott	Version	v1

SHARED CARE PROTOCOL

for the use of

GnRH ARGONISTS

In

CENTRAL PRECOCIOUS PUBERTY

(CPP)

ROYAL BERKSHIRE HOSPITAL

READING

SHARED CARE PROTOCOL FOR GONADOTROPHIN RELEASING-HORMONE (GnRH ANALOGUE THERAPY)

Central precocious puberty (CPP) is a form of premature sexual maturation, with the early appearance of secondary sexual characteristics –

In girls - Breast development before 8 years of age.
Menarche before 9 years of age.

In boys - Genital development (including testicular enlargement) before 9 years of age.

These definitions based on established normal ranges.

- In girls the diagnostic age limit for breast development (Tanner Stage B2) corresponds to – 2.5 to 3.0 SD from the mean, and for menarche – 4SD.
- In boys the limit of Tanner Stage G2 corresponds to approximately – 2.5 SD.

There has, however, been a secular trend downwards in the age of puberty, and it has now been suggested that the cut-off age of precocious puberty for girls should be reduced to 7 years (and 6 years in those of Afro-Caribbean origin).

Other features of precocious puberty are:

- Development of pubic and axillary hair.
- Tall stature, especially in relation to parental heights.
- Rapid growth rate.
- Advanced skeletal maturation (assessed using bone age).

Important points

- CPP is due to premature activation of the hypothalamo-pituitary axis, and consequently not only the pattern, but also the consonance of puberty in CPP is the same as that seen in normal puberty.
- CPP almost certainly represents a spectrum of disease from a normal variant to

rapidly progressive disease.

The estimated incidence is 1 in 5,000 to 10,000.

CAUSES OF CPP:

Idiopathic: Sporadic, familial (the majority of cases especially in girls).

Organic

Hypothalmic hamartoma

CNS tumours: Astrocytoma, craniopharyngioma, ependymona, glioma,

pinealoma.

CNS malformations: Arachnoid cyst, supracellar cyst, phakomatosis,

hydrocephalus, septo-optic dysplasia.

Acquired disease: CNS infections, CNS abscess, radiation, chemotherapy, trauma.

Other: Adoption from abroad, abuse.

Overall, 90% of affected patients are female.

Idiopathic CPP occurs in only 30% of males, but in up to 80% of females.

There is overlap in the clinical and biochemical features of idiopathic and organic

CPP. As a result it is currently recommended that patients with CPP usually have MRI scanning of the brain (including pituitary and hypothalamus). Occult intra-cranial tumours are found in 4.8 – 13.3% of girls and 19.2% of boys with CPP.

HISTORY:

Age at presentation, growth, progression and development of pubertal and other

features.

FAMILY HISTORY:

Heights, ages at puberty of parents.

EXAMINATION:

Height, weight, pubertal staging, other features suggestive of underlying disease.

INVESTIGATIONS:

HORMONES: Beta HCG, freeT4, TSH, prolactin

LH and FSH (during iv. GnRH test).

Oestradiol and/or testosterone.

RADIOLOGY:

Bone Age

Pelvic Ultrasound (in girls)

MRI scan of head (including pituitary & hypothalamus).

Problems arising from CPP

- Social and psychological problems of tall stature, early developmental (and menarche).
- Loss of final height.

The aims of treatment are, therefore, to hold pubertal development in an emotionally immature child.

Indications for therapy

a) True precocious puberty due to premature activation of the hypothalamic-pituitary-gonadal axis.

b) Where puberty needs to be delayed in order to maximise growth potential e.g. growth hormone deficient children following cranial irradiation, congenital adrenal hyperplasia.

Gonadotrophin releasing-hormone analogues.

These are used in paediatric practice for the suppression of precocious puberty. There are four preparations currently available:

1. Buserelin.
2. Leuprorelin.

3. Goserilin

4. Triptorelin.

Buserelin

This is administered by nasal spray, and absorption is variable and it is not used locally.

Drug	**Leuprorelin**	**Goserelin**	**Triptorelin**
Name	**Prostap**	**Zoladex**	**Gonapeptyl**
Manufacturer	**Wyeth**	**Astra Zeneca**	**Ferring**
Preparation	**Microsphere**	**Depot pellet**	**Microsphere suspension**
Licensed in CPP	**No**	**No**	**Yes**
Injection site & route	**Abdomen – sc Buttock, thigh – im.**	**Abdomen, buttock - Sc.**	**Abdomen – sc. Buttock, thigh – im.**
3 – 4 weekly	**Yes**	**Yes**	**Yes**
10 – 12 weekly	**Yes**	**Yes**	**Yes**
Cost:	**£125**	**£84**	**£85**
Long acting	**£376**	**£267**	**£207**
Needle bore (gauge)	**23g (sc) 21g (im.)**	**16g. (3.6 mg) 14g. (10.8mg)**	**22g (sc.) 21g (im.)**

- All are available in 3-4 weekly preparations and also 10-12 weekly long acting long acting preparations.
- Only triptorelin (Gonapeptyl Depot and Decapeptyl SR) are currently licensed in CPP. The former is given 4 weekly initially and the later 3 monthly
- As Prostap and Gonapeptyl are microsphere suspensions, smaller doses can be administered in young children. The sc rather than the im. is preferable in all children with these preparations, as this is less painful.
- Goserelin is painful and unpleasant so is not used locally for CPP.

- **Gonapeptyl dose.**

    1. Body weight over 30 kg- initially 3.75 mg every 2 weeks for 3 doses, then every 4 weeks.

    2. Body weight 20-30 kg- initially 2.5 mg every 2 weeks for 3 doses, then every 4 weeks.

    3. Body weight under 20 kg- initially 1.875 mg every 2 weeks for 3 doses then every 4 weeks

    - Discontinue when bone maturation consistent with age; over 11 years in girls or over 12/13 years in boys.

Mode of action of GnRH agonists

All of these drugs are synthetic analogues of naturally occurring gonadotrophin releasing hormone (GnRH) which possess greater potency than the natural hormone, binding to the GnRH receptor. As a result there is an initial period of stimulation, which is often blocked using the anti-androgen cyproterone acetate, given (usually) for the first six weeks of therapy at a dose of 70 mg/m2/day.

Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid production. These effects are reversible on discontinuation of therapy.

Assessment of response to therapy

Development of secondary sexual characteristics, uterine/ovarian size, growth rate & bone maturation should be monitored clinically, sonographically & radiologically.

- If uncertain the best single test is probably GnRH stimulation.
- Basal serum testosterone levels may be useful in boys, but conversely oestradiol appears not to be as useful in girls

GnRH analogue side-effects

- Weight gain
- Local irritation: at the injection site with sc. or im. analogues (the injection site should be varied periodically), or nasal irritation with buserelin.

- As a result of suppression of the gonadal axis e.g. hot flushes and mood swings.
- Hypersensitivity: rashes, pruritus, asthma & rarely anaphylaxis.
- Others: headache, visual disturbance, dizziness, arthralgia/myalgia, hair loss, peripheral oedema, GI disturbances, sleep disorders.

Referral criteria

a) Children with precocious puberty (premature sexual maturation) should be referred to Dr Nick Mann, in the Growth/Endocrine Clinic at RBH.

b) Children should not be placed on GnRH analogue therapy before specialist evaluation has been completed.

c) Once the diagnostic criteria for CPP amenable to GnRH analogue therapy have been satisfied, consultant and GP should agree a strategy for shared care appropriate for each child.

d) The consultant will recommend commencing a GnRH analogue at an appropriate dose, and will provide the GP with a full report justifying GnRH analogue therapy.

Guidelines for shared care strategy

a) When initially commenced on a GnRH analogue, a child with precocious puberty will require more frequent hospital supervision to ensure an adequate response.

b) Once stabilised, a child with precocious puberty with no other medical problems does not require frequent hospital supervision and may remain the primary responsibility of the GP.

c) A minority of candidates for GnRH analogue therapy have, or continue to have complex health disorders requiring specialist management, e.g. following cranial irradiation. GP and specialist must discuss each case in order to agree a treatment and shared care strategy.

GP responsibilities

a) Providing family with advice on the need for investigation of the child's precocious puberty.

b) Prescribing the GnRH analogue when this is part of a shared care agreement.

c) Arranging that someone from the practice will be available to administer the second and subsequent injections.

d) Reporting adverse effects of therapy to specialist or deputy.

e) Liaising with endocrine specialist to agree long-term therapy based on predicted benefit.

Endocrine specialist responsibilities

a) Arranging for the first injection to be given by the endocrine clinic specialist nurse Christine Desmond.

b) Reviewing patient's pubertal development, growth and response to treatment at 3 to 6 monthly intervals. Monitoring will include height and weight measurements, pubertal staging, bone age assessment at approximately 12 monthly intervals, and hormone measurements as indicated.

c) Advising GP as to continued justification for GnRH analogue therapy.

d) Reviewing associated drug therapy.

e) Auditing patient's response to GnRH analogue therapy compared to nationally agreed criteria

Duration of therapy

Once started, treatment is generally continued until an age when puberty can be allowed to re-commence. This will vary with each child, but will tend to be at around 10-11 years of age.

In terms of height with GnRH agonist therapy:

- Final height is increased in treated patients compared to pre-treatment, and also untreated patients.
- GnRH agonist treatment does not improve FH in girls beyond 8 years of age.
- Results are not as goon in boys as girls.

However

- 75% of patients reach their genetic target height range.
- 40% reach their individual target height range.

- More than 90% of females have a final height > 150 cm.

Complete reversibility of hypothalamo-pituitary-gonadal axis has been demonstrated after discontinuation of therapy. Fertility & pregnancy outcome are unaffected in women (although an increase in polycystic ovarian syndrome (PCOS) has been described in some. Spermatogenesis is unaffected in men.

Contact Details

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Shared Care Agreement

I agree to your request to prescribe triptorelin for our patient …….. in accordance with the shared care guidelines which I have received.

Signed …… (GP)

Name ……..…..

Date ……..

Please sign and send a copy back to Dr Nick Mann, Department of Paediatrics, Royal Berkshire Hospital, Reading RG1 5AN.

12/12/2012