

**triptorelin 3.75mg depot injection (Gonapeptyl Depot[®]) No.
(160/05)**

Ferring Pharmaceuticals

New indication: central precocious puberty

4 March 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: a full submission

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.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

**Triptorelin 3.75mg depot
injection
(Gonapeptyl Depot®)**

Licensed indication under review treatment of confirmed central precocious puberty in girls under nine years and boys under ten years. It should only be used under the supervision of an appropriate specialist having facilities for regular monitoring of response.

Dosing information under review 3.75mg for children weighing more than 30kg, 2.5mg for children weighing between 20kg and 30kg and 1.875mg for children weighing less than 20kg by subcutaneous or by intramuscular injection every two weeks in the first month then every 28 days thereafter.

UK launch date May 2003

Comparator medications

Triptorelin (Gonapeptyl Depot®) is the only medicine licensed in the UK for the treatment of central precocious puberty. The other triptorelin preparation, Decapeptyl SR®, is not licensed for this indication. Scottish paediatricians advise that other gonadotrophin-releasing hormone (GnRH) analogues are used, but are not licensed for the treatment of this condition.

Cost per treatment period and relevant comparators

Annual treatment cost is £1105 (£1190 in the first year).

Summary of evidence on comparative efficacy

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 the first two studies this was defined as appearance of secondary sex characteristics before 8 years in girls and 9 years in boys, accelerated growth rate during the last 6 months, bone age at least one year greater than chronological age, pubertal response to GnRH and sex hormones levels above the prepubertal range. Inclusion criteria were not provided for the third study. In the first study, 33 girls and 6 boys, were treated for up to 2 years; in the second study, which recruited 66 girls and 7 boys, treatment continued for at least 2, 3 and 4 years in 58, 23 and 10 patients, respectively; and in the third study 28 girls and 2 boys received treatment for up to 7 years. A primary outcome was not identified for these studies. In all trials serum gonadotrophin levels decreased from baseline and puberty stopped or regressed in most patients. The ratio of change in bone age to change in chronological age, was elevated at baseline to mean values of 2.29 and 1.37 in the latter two respective trials. It was reduced to 0.59 and 0.57 after 2 years' treatment in the first two studies and was 0.5 during therapy in the third trial.

An open-label study included 50 girls with central precocious puberty, defined as secondary pubertal signs before 8 years, accelerated growth rate, change in bone age to change in chronological age ratio >1.2 and pubertal response to GnRH. They received triptorelin depot injection for a mean duration of about 4.5 years (range 1 to 9.7 years) and had a mean final

height of 161cm, which was significantly higher than mean predicted adult height (estimated via the Bayley and Pinneau method) at the start of treatment, 155cm.

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 first of these trials included a group of 10 girls with central precocious puberty (defined as pubertal signs before 8 years, bone age more than one year greater than chronological age, pubertal response to luteinizing hormone-releasing hormone and uterus longitudinal diameter >3.5cm) who refused treatment plus 30 girls who were randomised to buserelin intranasal spray 35mcg/kg/day in three equal doses or to triptorelin 60mcg/kg every 28-days. 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.

Summary of evidence on comparative safety

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 clinical effectiveness issues

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 comparative health economic evidence

The manufacturer states that the product is cheaper and at least as effective as any alternative. While relative costs were estimated these were not based on approved doses as the alternative treatments are not licensed for this condition.

Budget impact

The manufacturer estimates that there is a potential saving of £45k on the drugs budget.

Guidelines and protocols

The 2004 Scottish Intercollegiate Guidelines Network (SIGN) publication number 76 on the long term follow up of survivors of childhood cancer note that cranial or craniospinal radiotherapy following surgical excision of brain tumours leaves survivors at high risk of growth hormone deficiency. In a significant minority there will be additional pituitary hormone deficiencies, which contribute to reduced growth. In addition, both boys and girls may have an early onset of puberty, which may be precocious in girls. The younger the age at irradiation, the earlier the onset of puberty. It is recommended that prepubertal girls receiving cranial radiotherapy should be closely monitored for clinical signs of precocious puberty. Causes of

poor growth, other than growth hormone deficiency, including deficiencies of other pituitary hormones or problems related to early or delayed puberty, should be considered and treated as necessary.

The 2004 British Society for Paediatric Endocrinology and Diabetes shared care protocol for the use of GnRH agonists in central precocious puberty notes that treatment is indicated for true precocious puberty due to premature activation of the hypothalamic-pituitary-gonadal axis and where puberty needs to be delayed in order to maximise growth potential, e.g. growth hormone deficient children following cranial irradiation or congenital adrenal hyperplasia. The protocol notes that GnRH analogues are used in paediatric practice for the suppression of precocious puberty and that the following are available: buserelin, leuprorelin, goserelin and triptorelin. It also notes that only triptorelin is licensed for treatment of central precocious puberty, but does not make any recommendation about which drug should be used, except that buserelin should be reserved for those unable to tolerate the other drugs.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 11 February 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

Drop SLS, Odink RJH, Oostdijk W et al. Clinical trial report. A multicentre study of D-Trp6-LHRH microspheres (Decapeptyl controlled release) in the treatment of true precocious puberty. October 1992.

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Heger S, Partsch CJ and Sippell WG. Long-Term Outcome after depot gonadotrophin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab 1999; 84: 4583-90.

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