Scottish Medicines Consortium

histrelin acetate, 50mg subcutaneous implant (Vantas®)
No. (557/09)

Orion Pharma (UK) Ltd

05 June 2009 *(issued 10 July 2009)*

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: following a full submission

histrelin (Vantas®) subcutaneous implant is accepted for restricted use within NHS Scotland for palliative treatment of advanced prostate cancer. Histrelin is restricted to use in patients with an anticipated life expectancy of at least one year in whom annual administration will offer advantages.

In a single-arm study, histrelin provided effective suppression of testosterone levels in patients with advanced prostate cancer. It requires less frequent administration than other leutenising hormone releasing hormone (LHRH) agonists. Other LHRH agonists are available at a lower acquisition cost.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Palliative treatment of advanced prostate cancer.

Dosing information

One 50mg implant administered every 12 months. An average of 50micrograms histrelin acetate is delivered daily. The implant is inserted subcutaneously in the inner aspect of the upper arm. The implant must be removed after 12 months of treatment. At the time the implant is removed a new implant may be inserted in order to continue the treatment.

Product availability date

June 2009

Summary of evidence on comparative efficacy

Testosterone is essential to the growth and perpetuation of prostate tumour cells and luteinising hormone releasing hormone (LHRH) agonists initially stimulate and then suppress testicular androgen production. This can result in 'chemical castration' that is an alternative to surgical castration in advanced prostatic carcinoma. Histrelin is a novel LHRH agonist formulated as an implant allowing once-yearly administration.

Histrelin was assessed in a pivotal phase III open-label, single-arm, multi-centre study performed in 138 patients with advanced prostatic carcinoma. Mean age was 75 years and 90% of patients were aged over 65 years. A single histrelin 50mg implant was administered subcutaneously and kept in place for 52 weeks. The primary endpoints were attainment of serum testosterone levels indicative of chemical castration (<50ng/dL) at four weeks after implantation and the maintenance of those levels at 52 weeks. The implant was changed after one year and patients were followed at pre-defined endpoints up to week 60 for the pivotal study and thereafter for a follow-up study. Concomitant androgen and anti-androgen therapy, including orchiectomy, was not permitted.

Patients were included in an efficacy-evaluable analysis if they were either deemed a treatment failure or completed the entire 52-week protocol. An observed-cases analysis included all those with an evaluable sample at any particular endpoint. There was no imputation for missing values, and patients discontinuing for reasons not related to lack of efficacy were excluded from the analyses.

At four weeks all efficacy-evaluable patients (n=111) and all observed cases (n=134) had attained medical castration and this was maintained in all eligible patients at 52 weeks in both analyses (n=111 and n=115 respectively). The proportion of eligible patients in either analysis who maintained castration testosterone levels between four and 52 weeks was 100% at most pre-defined endpoints and never less than 99%. Following a transient increase ('flare'), testosterone levels decreased within about two weeks and, apart from one assessment, were below a threshold of 20ng/dL in more than 99% of evaluable patients at week four and thereafter.

Measurements of associated biochemical markers (LH and prostate-specific antigen) showed patterns consistent with suppression of testosterone; more than 84% of patients reported no change in analgesic requirement or consumption, and the only notable findings from an exploratory disease-specific quality of life questionnaire were an increase in fatigue and decrease in sexual function.

In the extension study there was no acute on chronic 'flare' of testosterone levels on re-insertion of a second implant, and small numbers of patients continued up to a fourth implant with maintenance of castration testosterone levels and a safety profile similar to that in the first year of treatment.

The results of the pivotal study were supported by a second phase III study in which 59 patients received histrelin implant or goserelin, but which was discontinued during enrolment and was not considered pivotal.

Summary of evidence on comparative safety

The comparative study versus goserelin that was discontinued during enrolment provided only limited data but suggested a similar adverse event profile for histrelin and goserelin. In the pivotal study the adverse event profile was representative of this class of agent in an elderly population and of subcutaneous administration. Problems of loss or ejection of the implant device were mainly confined to earlier designs rather than the product being marketed. Within the overall clinical programme for histrelin, 84 patients received the final marketed design for up to a year, representing approximately half of the patients exposed to histrelin.

Summary of clinical effectiveness issues

The pivotal and supportive phase III studies were both initiated as comparative studies versus other LHRH agonists, but protocols were modified with the approval of the U.S. Food and Drug Administration to convert the pivotal study to a single-arm design and to discontinue the second during enrolment. Commenting on the relative lack of comparative data, the European Medicines Agency has stated that comparative studies for histrelin with other LHRH agonists would be superfluous for licensing purposes.

In the pivotal study there was no method of imputation for missing observations for primary and secondary endpoints. The observed cases analysis included patients with an evaluable observation at any of the pre-specified endpoints, while the efficacy evaluable analysis excluded patients without observations at both four and 52 weeks. Patients who discontinued for reasons other than lack of efficacy were excluded from the analyses.

British, U.S. and European guidelines support the use of chemical castration with LHRH agonists as a first-line choice in advanced prostatic cancer, providing an alternative to surgical castration. Antagonists of LHRH provide an alternative hormonal therapy: they have less well-established efficacy and cause gynaecomastia, but may have advantages in terms of sexual function. Diethylstilbestrol is an alternative agent for medical castration but concerns about cardiotoxicity limit its usefulness. Choice of therapy should be individualised according to patient concerns and preference.

Guidelines recommend the use of concomitant anti-androgen therapy around the time of initiation of LHRH agonist therapy as prophylaxis against clinical flare arising from increased testosterone secretion in the first few days of therapy. Concomitant anti-androgen therapy was not permitted in the pivotal histrelin study. It is not clear whether this influenced the adverse event profile, and the histrelin Summary of Product Characteristics only advises prophylactic anti-androgen therapy to be considered for patients with metastatic vertebral lesions and/or urinary tract obstruction.

It is generally acknowledged that there are insufficient comparative data between different LHRH agonists (including histrelin) to identify whether any one agent is preferred over others. Convenience and frequency of administration may influence final choice. As administration of histrelin involves a minor surgical procedure, training will be necessary and this may have implications for service delivery compared with alternative treatments: most other LHRH agonists (including goserelin implant) are administered three-monthly by subcutaneous or intramuscular injection in the general practice setting. Annual administration of the implant may be a disadvantage with regard to the reversibility of adverse effects. Some other LHRH agonists also have a broader range of indications in patients with advanced disease e.g. as adjuvant and neo-adjuvant therapy.

Summary of comparative health economic evidence

The manufacturer presented a simple cost-minimisation analysis comparing a once-yearly implant of histrelin acetate to goserelin 10.8mg every 12 weeks and to triptorelin 11.25mg every 3 months. These comparators were appropriate given prescribing patterns in Scotland which show goserelin to be the most frequently prescribed agent. A one-year time horizon was chosen which seemed reasonable if eligible patients are those who are assumed to have a life expectancy of at least one year.

Clinical data to support the assumed clinical equivalence between treatments, as required for a cost-minimisation analysis to be appropriate, were largely by assumption and by relying on the class effect of the drugs based on the ability to achieve castration levels of serum testosterone. The only costs in the analysis were the drug acquisition costs of the three treatments. No allowance was made for staff time or consumables used to administer the treatments.

The results indicated that the annual cost associated with histrelin acetate was £990 per patient compared to £1,157 for goserelin and £828 for triptorelin. As such, histrelin would be preferred on cost-minimisation grounds to goserelin but not triptorelin.

The analysis was generally sufficient to support histrelin acetate as being a cost-effective treatment option but several limitations of the analysis should be noted:

- There was a lack of good quality data to compare the treatments under consideration;
- The time horizon was appropriate when considering patients with at least a one year life expectancy but it should be borne in mind that for patients whose expected survival is less than one year, the other treatments would be preferred on cost-minimisation grounds;
- Staff time and consumable costs, which may be higher with histrelin on a per administration basis, were excluded from the analysis but it is unlikely that this would have a material effect on the results given the less frequent administration needed with histrelin compared to the three monthly injections.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In February 2008, the National Institute for Health and Clinical Excellence published a guideline entitled 'Prostate cancer: diagnosis and treatment.'

In March 2007 the European Association of Urology published an updated guideline entitled 'Guidelines on prostate cancer.'

In December 2008, the National Comprehensive Cancer Network published version 1.2009 of an NCCN Clinical Practice Guideline in Oncology for prostate cancer.

Relevant recommendations, including those relating to LHRH agonists, are summarised in the clinical effectiveness section of this document. None give specific recommendations about histrelin.

Additional information: comparators

Androgen withdrawal therapy for advanced prostate cancer may take the form of surgical castration (bilateral orchiectomy) or chemical castration with long-acting LHRH agonists which include buserelin, goserelin, leuprorelin or triptorelin as well as histrelin.

Medical castration with oestrogenic therapy (diethylstilboestrol) is also licensed in advanced prostatic carcinoma, and anti-androgens that antagonise effects at the androgen receptor (bicalutamide, cyproterone acetate, flutamide) may be appropriate for selected patients.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£) Cost per course (£)
Histrelin acetate implant 50mg	**One implant every 12 months**	**990**
Bicalutamide tablets 150mg	150mg daily	2193
Buserelin nasal spray (Suprefact)	One 100 microgram spray into each nostril six times daily	1324*
Goserelin implant 10.8mg	One implant every 12 weeks	1159
Goserelin implant 3.6mg	One implant every 28 days	1094
Triptorelin injection 3.75mg (Gonapeptyl depot)	One injection every 28 days	1062
Diethystilboestrol tablets 1mg	1 to 3mg daily	507 to 1521

Cyproterone acetate tablets 100mg	200 to 300mg daily	672 to 1008
Leuprorelin acetate injection 3.75mg	One injection every 28 days	978
Leuprorelin acetate injection 11.25mg	One injection every 3 months	903
Triptorelin injection 3mg (Decapeptyl SR)	One injection every 28 days	897
Triptorelin injection 11.25mg (Decapeptyl SR)	One injection every 3 months	828
Flutamide tablets 250mg	250mg three times daily	300

* Cost in first year would also include induction with buserelin injection 500micrograms every 8 hours for 7 days: Combined cost for first year = £1600

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 April 2009 except for histrelin which is a provisional cost provided by the sponsor company.

Additional information: budget impact

The manufacturer presented two scenarios in terms of the net budget impact of introducing histrelin acetate. The first scenario examined what would happen if histrelin took its market share from current prescribing of goserelin. Goserelin is the most frequently prescribed current treatment according to the manufacturer's sales data and histrelin has a cost advantage over this agent. In this scenario, the net drug budget impact was a projected saving of £13k in 2010 rising to a saving of £63k by 2014. In the second scenario, the market share for histrelin was obtained from reduced prescribing of triptorelin, which has a lower annual acquisition than histrelin. The projections in this scenario were for increased costs of £13k in 2010 rising to increased costs of £64k in 2014. The manufacturer's estimates do not take account of any staff costs associated with the administration of the treatment.

In each scenario, 7,623 patients were assumed to be eligible and receiving LHRH agonists in 2010 rising to 7,720 patients by 2014. However, the focus of the budget impact analysis was only on the proportion of this patient population who were being treated with either goserelin or triptorelin, which was a stable 67% of eligible patients across the time horizon. Both sets of calculations assumed that 1% of patients would be prescribed histrelin in year one rising to 5% by year five.

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 08 April 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Schlegel PN. Efficacy and safety of histrelin subdermal implant in patients with advanced prostate cancer. J Urol 2006;175:1353-58.

The Euoropean Medicines Agency (EMEA) Committee for Medicinal Products for Human Use CHMP Vantas Evaluation, Annex II - Scientific conclusions. 2007. Available at: http://www.emea.europa.eu

Center for Drug Evaluation and Research, Approval Package for Application Number NDA 21-732, Medical Review. FDA. 2004. Available at http://www.fda.gov/cder