NHS Herefordshire Clinical Commissioning Group

Wye Valley NHS Trust

HEREFORDSHIRE SHARED CARE GUIDELINE FOR DEGARELIX

Introduction

Prostate cancer is a sporadic cancer affecting 32,000 men each year in the United Kingdom. It can be confined to the prostate (localised), extend locally beyond the prostatic capsule or into the seminal vesicles (locally advanced) or can be metastatic.

Radiotherapy, surgery, active surveillance, brachytherapy and hormone manipulation therapy are treatment options for localised disease. Locally advanced disease can be treated with a combination of radiotherapy and hormone therapy or hormone therapy alone.

The usual management of advanced hormone-dependent prostate cancer is with hormone therapy (medical castration) alone or surgical castration. Medical castration is achieved by Luteinising Hormone Releasing Hormone (LHRH) agonists such as goserelin, leuprorelin or triptorelin or the Gonadotrophin Releasing Hormone (GnRH) antagonist, degarelix.

Degarelix is a selective GnRH antagonist at pituitary GnRH receptors. It reduces the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and thereby reduces the secretion of testosterone (T) by the testes. Unlike LHRH agonists, GnRH antagonists do not induce a LH surge with subsequent testosterone surge/tumour stimulation and potential symptomatic flare after the initiation of treatment.

Shared Care

- This shared care agreement has been produced following the inclusion of degarelix on the Herefordshire Formulary in the treatment of prostate cancer. Shared care has been defined as the mechanism of sharing patient care between primary and secondary care providers. This document sets out these responsibilities from initial diagnosis to on going support.
- In the Guidelines for Responsibility for prescribing between hospitals and GPs (circular EL (91)127), the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Indication for Therapy

Patients with metastatic prostate cancer and many with locally advanced non-metastatic prostate cancer are treated with gonadorelin (LHRH) agonists to render them castrate. The first dose of LHRH agonist requires short-term cover with an anti-androgen to avoid 'tumour flare' and castrate levels of testosterone are achieved in 20% and 96% of patients by 14 and 28 days respectively [1]. For most cases, this is a sufficiently fast response. However, a minority of symptomatic patients require a more rapid lowering of testosterone. Under these circumstances, medical castration using degarelix (a GnRH antagonist) or surgical castration if feasible are indicated. Following degarelix administration, 96% of patients have castrate levels of testosterone within 3 days compared with 0% on a LHRH agonist [1]. The first dose of degarelix does not require concomitant anti-androgen cover.

LHRH agonists are currently prescribed using shared care arrangements, allowing patients to receive doses in primary care. A similar arrangement should be feasible for degarelix.

[1] Klotz L *et al*. The efficacy and safety of degarelix: a 12-month comparative randomised open-label parallel-group phase III study in patients with prostate cancer. BJU Int 2008; 102: 1531-8

Treatment Aim

It is proposed to use degarelix for the treatment of adult male patients with advanced hormone-dependent prostate cancer to achieve a rapid lowering of testosterone. These symptomatic metastatic patients with a PSA >20ng/ml will present with symptoms such as:

- impending spinal cord compression (as per NICE Clinical Guideline 75)
- renal failure due to ureteric obstruction
- severe symptoms warranting hospitalisation e.g. bone pain

Degarelix is also suitable for patients where LHRH agonists are contraindicated such as patients with liver dysfunction or metabolic bone disease, as well as patients who can not

tolerate or are allergic to anti-androgens to suppress the testosterone surge associated with LHRH agonist use.

Dose

Starting dose (hospital):
240 mg administered as two subcutaneous injections of 120 mg each in secondary care.
Maintenance dose (monthly administration by GP):
80 mg administered as one subcutaneous injection in primary care.
The first maintenance dose should be given one month after the starting dose and monthly thereafter for the rest of the man's life.

Preparation and Availability

Degarelix 80mg vial (1 vial)
Degarelix 120mg vial (2 vial pack = 240mg)

Both preparations are licensed products with further information available at –

http://www.medicines.org.uk/emc/searchresults.aspx?term=degarelix+acetate&searchtype=QuickSearch

Contraindications, precautions and warnings

***Contraindications*:**
Hypersensitivity to the active substance or to any of the excipients.

Precautions and warnings:
Effect on QT/QTc interval
Long-term androgen deprivation therapy may prolong the QT interval. In the confirmatory study comparing FIRMAGON to leuprorelin periodic (monthly) ECGs were performed; both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients, and 500 msec in 1% and 2% of the degarelix and leuprorelin patients, respectively.

FIRMAGON has not been studied in patients with a history of a corrected QT interval over 450 msec, in patients with a history of or risk factors for torsades de pointes and in patients receiving concomitant medicinal products that might prolong the QT interval.

Hepatic impairment
Patients with known or suspected hepatic disorder have not been included in long-term clinical trials with degarelix. Mild, transient increases in ALT and AST have been seen, these were not accompanied by a rise in bilirubin or clinical symptoms. Monitoring of liver function in patients with known or suspected hepatic disorder is advised during treatment. The pharmacokinetics of degarelix has been investigated after single intravenous administration in subjects with mild to moderate hepatic impairment.

Renal impairment
Degarelix has not been studied in patients with severe renal impairment and caution is therefore warranted.

Hypersensitivity
Degarelix has not been studied in patients with a history of severe untreated asthma, anaphylactic reactions or severe urticaria or angioedema.

Changes in bone density
Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist. It can be anticipated that long periods of testosterone suppression in men will have effects on bone density. Bone density has not been measured during treatment with degarelix.

Glucose tolerance
A reduction in glucose tolerance has been observed in men who have had orchiectomy or who have been treated with a GnRH agonist. Development or aggravation of diabetes may occur; therefore diabetic patients may require more frequent monitoring of blood glucose

when receiving androgen deprivation therapy. The effect of degarelix on insulin and glucose levels has not been studied.

Side Effects

- *Uncommon*: hypersensitivity, hyperglycaemia/diabetes mellitus, cholesterol increased, weight decreased, appetite decreased, changes in blood calcium, depression, decreased libido*, mental impairment, hypoaesthesia, vision blurred, cardiac arrhythmia (including atrial fibrillation), palpitations, QT prolongation*, hypertension, vasovagal reaction (including hypotension), dyspnoea, constipation, vomiting, abdominal pain, abdominal discomfort, dry mouth, bilirubin increased, alkaline phosphatase increased, urticaria, skin nodule, alopecia, pruritus, erythema, osteoporosis/osteopenia, arthralgia muscular weakness, muscle spasms, joint swelling/stiffness, pollakiuria, micturition urgency, dysuria, nocturia, renal impairment, incontinence, testicular pain, breast pain, pelvic pain, genital irritation, ejaculation failure, malaise, peripheral oedema.

- *Common:* anaemia*, weight increase*, insomnia, dizziness, headache, diarrhoea, nausea, liver transaminases increased, hyperhidrosis (including night sweats)*, rash, musculoskeletal pain and discomfort, gynaecomastia*, testicular atrophy, erectile dysfunction*, chills, pyrexia, fatigue*, Influenza-like illness.

- *Very common:* Hot flush*, injection site adverse events.

* known physiological consequence of testosterone suppression

Monitoring

Pretreatment (see Consultant request letter to GP for these results).

Toxicity

Parameter	Frequency of Monitoring	Result	Action
Blood Pressure			
ECG		Increased QT interval	
Glucose			
U&E			
LFT		Transient rises may be seen	
Dyspnoea,cough,			

Efficacy

Parameter	Frequency of Monitoring	Result	Action
PSA	3 to 6 month intervals	Increase of >50% from nadir	Refer to secondary care
Testosterone <0.5ng/ml	3 to 6 month intervals	>0.5ng/ml	Refer to secondary care

Interactions

No formal drug-drug interaction studies have been performed.
Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of degarelix with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, cisapride, moxifloxacine, antipsychotics, etc. should be carefully evaluated.
Degarelix is not a substrate for the human CYP450 system and has not been shown to induce or inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 to any great extent *in vitro*. Therefore, clinically significant pharmacokinetic drug-drug interactions in metabolism related to these isoenzymes are unlikely.

Recommendations to GP

- Confirm or decline request to share patient's care as soon as possible
- Monitoring the patient's overall health and well being and observing patient for evidence of ADRs/abnormalities and raising with secondary care clinician if necessary
- Blood tests (Serum PSA +/- bone profile, U+Es, liver function tests, full blood count) should be measured at intervals as specified by secondary care
- No other specific monitoring requirements
- Further prescription and administration of maintenance 80 mg dose of degarelix after initiation by secondary care and continued prescription and administration of degarelix unless advised to stop treatment by secondary care
- If a patient misses his degarelix injection by more than 2 weeks, he should be given the initiation dose of 240 mg degarelix and then follow the monthly 80 mg degarelix schedule thereafter
- Arranging for regular administration by the practice or district nurse
- Ensuring advice is sought from the secondary care clinician if there is any significant change in the patient's physical health status

Cost

Degarelix 240mg (2 x 120mg) Induction dose ~~£2~~260.00 (ex. VAT)
Degarelix 80mg Maintenance dose (monthly) ~~£1~~29.37 (ex.VAT)

Ferring will rebate 30% of the PCO spend on Degarelix prescriptions in primary care:
Degarelix 240mg (2 x 120mg) Induction dose **~~£1~~76.12 (ex. VAT)**
Degarelix 80mg Maintenance dose (monthly) **~~£8~~9.00 (ex. VAT)**

Contacts – back up advice and support

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Other				