Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Angela Timoney FRPharmS
NHS SCOTLAND

vardenafil 10mg orodispersible tablet (Levitra®) SMC No. (727/11)

Bayer Healthcare

09 September 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

vardenafil orodispersible tablet (Levitra®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of erectile dysfunction (ED) in adult men. ED is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for vardenafil to be effective, sexual stimulation is required.

SMC restriction: use is restricted to patients in whom an orodispersible tablet is an appropriate formulation. Vardenafil is subject to the same NHS prescribing restrictions as other drug treatments for erectile dysfunction in terms of National Health Service (General Medical Services) (Scotland) regulations.

Two placebo controlled, studies have shown that vardenafil orodispersible is significantly better than placebo in the treatment of erectile dysfunction in men. No comparative evidence against other medicines for erectile dysfunction was presented.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of erectile dysfunction (ED) in adult men. ED is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Levitra to be effective, sexual stimulation is required.

Dosing Information

Vardenafil 10mg orodispersible tablet (ODT) is placed in the mouth on the tongue, to rapidly disintegrate, and is then swallowed. The ODT must be taken without liquid and immediately upon release from the blister. Vardenafil is taken when required, approximately 60 minutes before sexual activity.

Product availability date

July 2011

Summary of evidence on comparative efficacy

Vardenafil is a phosphodiesterase type-5 (PDE-5) inhibitor that restores impaired erectile function by increasing blood flow to the penis following sexual stimulation. SMC has already accepted vardenafil film coated tablets (FCT) as an alternative to other phosphodiesterase type-5 inhibitors in the treatment of erectile dysfunction (ED). A new orodispersible tablet (ODT) formulation of vardenafil has now become available. Although the submitting company requested that SMC consider both the FCT and the ODT formulations (as the price of the FCT has reduced), further assessment of a medicine that has already been accepted is not part of SMC's process, therefore only the ODT has been assessed. The company has requested that SMC consider vardenafil ODT when positioned for use as either first-line treatment in men with dysphagia or in all men as an appropriate second-line treatment option when FCT formulations are found to be inconvenient or indiscreet.

Two identically designed double-blind, multi-centre, randomised, placebo-controlled phase III studies (POTENT I and POTENT II) of vardenafil ODT were conducted in healthy men with (ED) for a period of six months or more, who were in a heterosexual relationship for at least six months and were highly motivated to receive ED treatment. POTENT I was carried out in Europe and South Africa and POTENT II in Australia, Canada, Mexico and the United States. Patients were randomised to treatment following a four-week run-in period in which eligible patients had to make at least four attempts at sexual intercourse on four separate days of which at least 50% were unsuccessful. Randomisation was stratified by age (18 to 64 years and ≥65 years) and patients were allocated in a 1:1 ratio to either; vardenafil (ODT) 10mg taken without water on demand one hour prior to intended sexual intercourse, up to a maximum of one dose daily; or an orodispersible placebo tablet.

There were three co-primary efficacy endpoints: the change in the erectile-function (EF) domain of the International Index of Erectile Function (IIEF) at week 12 compared to the score at baseline; and the success-rates of the patients in answering the Sexual Encounter Profile questions 2 (SEP2) and 3 (SEP3) relating to successful vaginal penetration and successful intercourse. The IIEF has been adopted by the World Health Organisation as the efficacy endpoint of choice in clinical studies investigating treatment of ED. A score ranging from 0 to 30 with 0 to 6 indicating severe dysfunction and 25 to 30 indicating no dysfunction for the IIEF-EF domain.

Secondary outcomes for the pivotal trials, POTENT I and POTENT II were performed for the intention to treat (ITT) population only and included the proportion of subjects achieving `return to normal' erectile function (IIEF-EF≥26) at last visit and Sexual Encounter Profile diary responses other than SEP2 and SEP3.

The POTENT I study randomised 362 patients to either vardenafil ODT 10mg on demand (n=186) or placebo (n=176). Vardenafil significantly improved ED, as measured by the IIEF-EF score, by difference in treatment effect of 7.1 (95% confidence interval [CI]: 5.7 TO 8.6). The POTENT II study randomised 339 patients to either vardenafil ODT 10mg on demand (n=172) or placebo (n=167). Vardenafil significantly improved ED by difference in treatment effect of 6.9 (95% CI 5.4 TO 8.5).

Pharmacokinetic studies comparing vardenafil ODT with vardenafil film coated tablets (FCT) demonstrated that the ODT are not bioequivalent. The bioavailability of the ODT formulation was 21 to 44% greater than the film coated vardenafil tablets.

Summary of evidence on comparative safety

Over the two phase III studies, adverse effects were experienced by 38% of patients randomised to vardenafil compared with 22% of patients randomised to placebo (relative risk 1.76). Many of the adverse effects were classified as being potentially related to the drug (63% of adverse effects in vardenafil patients versus 34% of those in placebo patients). Few adverse effects led to treatment discontinuation or were serious in nature. There were no deaths post-randomisation. In the first study there were four serious treatment-emergent adverse events in the vardenafil arm (all in patients ≥ 65years of age) and in the second study there were two severe treatment-emergent adverse effects reported. In both phase III studies there was a low discontinuation rate due to treatment-emergent adverse events for each group: vardenafil ODT (1.1% and 1.8%) and placebo (0.6% and 0.6%).

The European Medicines Agency (EMA) noted that the adverse events most frequently observed with vardenafil ODT: headache, flushing, nasal congestion, dyspepsia, and back pain were mild to moderate in intensity and consistent with the adverse event profile of vardenafil FCT.

Summary of clinical effectiveness issues

In two placebo-controlled phase III studies, vardenafil ODT was statistically and clinically significantly superior to placebo in improving erectile function in patients with ED. In the absence of direct comparative evidence for vardenafil against other PDE-5 inhibitors, a number of systematic reviews of PDE-5 inhibitors including vardenafil, sildenafil and tadalafil were included. These concluded that all PDE-5 inhibitors were highly effective and that there were no significant differences between treatments in terms of clinical effectiveness.

Pharmacokinetic studies demonstrate that vardenafil ODT 10mg has a 21 to 44% greater bioavailability than vardenafil FCT 10mg. The Summary of Product Characteristics notes that, due to this difference in bioavailability, ODT and FCT should not be considered as equivalent. The recommended daily dose of vardenafil FCT is 10mg but this can be increased to 20mg if necessary. The maximum daily dose for vardenafil ODT is 10mg. There are also some

differences in onset and duration of action that may lead to patient preference for a particular preparation. The ODT should be taken approximately 60 minutes before sexual activity whereas the FCT may be taken 25 to 60 minutes before sexual activity.

A limitation of the studies was the short duration of follow-up, 12 weeks.

As the FCT and ODT formulations are not bioequivalent, and there is no direct comparison of clinical outcomes between the two formulations, the relative efficacy of the vardenafil ODT and tadalafil and sildenafil has not been established. However, on request from the New Drugs Committee the company provided an indirect comparison that supported the comparable clinical effectiveness of vardenafil 10mg ODT and vardenafil 20mg FCT.

The submitting company proposed two different patient populations where vardenafil ODT may be of benefit; as a first line treatment option in men who have dysphagia or as a second line treatment in men who find conventional FCT formulations to be inconvenient or indiscreet. Clinical experts questioned the proposed positioning, stating that dysphagia is encountered rarely in men with ED and that the claimed advantages over FCT in relation to convenience and discretion in this patient population are unclear.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing vardenafil ODT 10mg to sildenafil FCT 50mg, vardenafil FCT 10mg and tadalafil FCT 10mg for two groups of patients with ED. These patient groups were either first-line treatment in men with dysphagia or as an appropriate second-line treatment option in men when FCT formulations are found to be inconvenient or indiscreet. These are sub-groups of the full licensed indication. The time horizon selected for the base-case was one year. The submitting company also presented analyses for the FCT formulation of vardenafil, but as SMC has previously issued recommended advice on this product, these analyses were not considered further.

The clinical evidence used as a basis for the cost-minimisation analysis came from five systematic reviews or meta-analyses concluding that vardenafil, sildenafil and tadalafil are all effective treatments with minimal differences between them.

The analysis compared the drug acquisition costs of each treatment only.

The results showed the cost per year was £232 per patient treated with vardenafil ODT 10mg and £188, £277 and £351 per patient treated with vardenafil FCT 10mg, sildenafil FCT 50mg and tadalafil FCT 10mg respectively. The submitting company therefore claimed that vardenafil ODT 10mg is less costly than sildenafil FCT 50mg and tadalafil FCT 10mg, and would thus be the preferred treatment on cost-minimisation grounds.

The sensitivity analysis varied the treatment frequency per year and altered the cost differences proportionally. No other sensitivity analyses were performed.

The New Drugs Committee had some concerns with the analysis as originally submitted. This related principally to the lack of a formal indirect comparison to underpin the assumption of equivalence between treatments. In addition there were concerns in relation to the positioning proposed by the company for the product. As noted above, the submitting company

subsequently provided an adjusted indirect comparison to support the economic case. While this may have some limitations, it was considered sufficient to conclude that the economic case was demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British Society for Sexual Medicine produced "Guidelines on the Management of Erectile Dysfunction" in 2009. These guidelines detail that the first line of treatment for ED should be oral pharmacotherapy in the form of a PDE-5 inhibitor. The PDE-5 inhibitors discussed in this guideline are sildenafil, tadalafil and vardenafil FCTs.

The European Association of Urology published guidelines in 2009: "Guidelines on Male Sexual Dysfunction: Erectile Dysfunction and Premature Ejaculation". These guidelines recommend oral pharmacotherapy in the form of PDE-5 inhibitors: sildenafil, tadalafil and vardenafil film-coated tablets. The guideline did not have a preference between the PDE-5 inhibitors due to lack of direct comparative studies. The choice of agent should be directed by the patient's personal experience and the frequency of intercourse and should take into account the duration of action and how to take the medicine.

Additional information: comparators

Relevant comparators licensed for the treatment of erectile dysfunction are; oral PDE-5 inhibitors (sildenafil, tadalafil, vardenafil film-coated tablets); and alprostadil administered either intracavernosally (Caverject®, Viridal® Duo) or by urethral application (MUSE®). Pharmacological treatment options are prescribable on the NHS under specific prescribing restrictions in the National Health Service (General Medical Services) (Scotland) Regulations 1995.

Non-pharmacological strategies include the use of vacuum devices, or surgical insertion of a penile prosthesis.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Vardenafil orodispersible tablet	**10mg taken orally on demand**	**232***
Tadalafil	10mg - 20mg taken orally on demand	351* - 351*
Sildenafil	50mg - 100mg taken orally on demand	277* - 305*
Vardenafil (film-coated tablet)	10mg - 20mg taken orally on demand	183* - 305*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 13 June 2011. * cost based on one dose taken per week.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 31,892 patients in year 1, rising to 40,415 by year 5. Based on an estimated uptake of 2.46% in year 1, rising to 6% in year 5, the medicines budget impact was estimated at £181k in year 1 and £558k in year 5. After taking account of the displacement of other treatments, the net medicines budget impact was estimated as a saving of £58k in year 1 rising to a saving of £181k in year 5.These figures assumed that each patient would receive one vardenafil dose per week.

References

The undernoted references were supplied with the submission.

Sperling H, Debruyne F, Boermans A, Beneke M, Ulbrich E, Ewald S. The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. J Sex Med 2010; 7(4 Pt 1):1497-1507.

Gittelman M, McMahon CG, Rodriguez-Rivera JA, Beneke M, Ulbrich E, Ewald S. The POTENT II randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. Int J Clin Pract 2010; 64(5):594-603.

European Medicines Agency. EPAR – for Levitra - vardenafil. Available from: http://www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 12 August 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.