NICE advice

Premature ejaculation: dapoxetine

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in May 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Dapoxetine is a short-acting selective serotonin-reuptake inhibitor (SSRI). It is the first pharmacological treatment for premature ejaculation to be licensed in the UK. In a pooled analysis of 4 randomised controlled trials (RCTs) in men with premature ejaculation there was a statistically significant increase in intravaginal ejaculatory latency time (IELT) with dapoxetine 'on demand' compared with placebo 'on demand', although an increase in IELT was also seen with placebo.

Effectiveness	Safety
• Statistically significant increase in IELT from baseline with dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' (from 0.9 minutes in all groups to 1.9, 3.1 and 3.6 minutes respectively for placebo, dapoxetine 30 mg and dapoxetine 60 mg; p<0.001 for comparisons with placebo, pooled analysis of 4 RCTs, n=4843). • Statistically significantly more men reported that their premature ejaculation was 'better' or 'much better' with dapoxetine compared with placebo (30.7% and 38.3% with dapoxetine 30 mg and 60 mg respectively compared with 13.7% with placebo; p<0.001 for comparisons with placebo, pooled analysis of 4 RCTs, n=4843).	• Orthostatic hypotension and syncope was reported in clinical trials and the summary of product characteristics includes recommendations to minimise the risk of this. • Treatment with dapoxetine should not be initiated with the 60 mg dose. The incidence and severity of adverse events is higher with the 60 mg dose.

User factors	Resource implications
• Men will need to be appropriately assessed and given an accurate diagnosis of premature ejaculation in line with the indication in the summary of product characteristics before dapoxetine can be considered. • Dapoxetine is taken 'on demand' approximately 1 to 3 hours before anticipated sexual activity. • The summary of product characteristics states that dapoxetine should not be used in men taking phosphodiesterase type 5 inhibitors (for example, sildenafil). • The summary of product characteristics states that a careful appraisal of the individual benefit/risk ratio should be carried out after the first 4 weeks of treatment (or at least after 6 doses of treatment) with dapoxetine to determine whether continuing treatment is appropriate. If dapoxetine is continued the benefit/risk balance should be re-evaluated at least every 6 months. • Men will need to balance the potential benefits with the likelihood of very common (greater than 1 in 10 men) adverse reactions of dizziness, headache and nausea reported in the summary of product characteristics.	• The cost of dapoxetine ranges from £14.71 for a pack of 3×30 mg tablets to £34.42 for a pack of 6×60 mg tablets. • The estimated cost of 30 days' supply of a longer-acting SSRI taken daily (off-label use) ranges from £0.94 to £6.38 depending on the SSRI used and the dosage.

Introduction and current guidance

In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), premature ejaculation is defined as a '*persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.*' The European Association of Urology 2014 guidelines on male sexual dysfunction state that although premature ejaculation is a very common male sexual dysfunction (with prevalence rates of 20% to 30%), the aetiology of premature ejaculation is unknown, with

little data to support suggested biological and psychological hypotheses. Despite the possible serious psychological and quality of life consequences of premature ejaculation, few men seek treatment.

Full text of Introduction and current guidance.

Product overview

Dapoxetine (Priligy) is licensed in the UK for the 'on demand' treatment of premature ejaculation in adult men aged 18 to 64 years. The summary of product characteristics states that dapoxetine should only be prescribed to men who meet all the following criteria:

- An intravaginal ejaculatory latency time (IELT) of less than 2 minutes **and**
- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the man wishes **and**
- Marked personal distress or interpersonal difficulty as a consequence of premature ejaculation **and**
- Poor control over ejaculation **and**
- A history of premature ejaculation in the majority of intercourse attempts over the prior 6 months.

The summary of product characteristics states that dapoxetine should not be prescribed to delay ejaculation in men who have not been diagnosed with premature ejaculation. The starting dose recommended in the summary of product characteristics for all men is 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity.

Full text of Product overview.

Evidence review

- This evidence summary is based on a pooled analysis of results from 5 phase III RCTs (McMahon et al. 2011) in men with premature ejaculation; 4 of the RCTs contributed to the main efficacy outcome. These 4 RCTs (n=4843) compared dapoxetine 30 mg and 60 mg 'on demand' with placebo 'on demand' for IELT (defined as the duration of time from penetration to intravaginal ejaculation and measured by a stopwatch held by the female partner during each intercourse episode).

- The pooled analysis showed that there was an increase from baseline in mean IELT at 12 weeks with all 3 groups including the placebo group. There was a statistically significantly greater increase from baseline in mean IELT at 12 weeks with both dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' (from 0.9 minutes in all groups to 1.9, 3.1 and 3.6 minutes respectively for placebo, dapoxetine 30 mg and dapoxetine 60 mg; $p<0.001$ for comparisons with placebo).

- Pryor et al. (2006) concluded that the minimum clinically important change in IELT seems to be about 1 minute based on a correlation of global impression of change scores with mean changes in IELT. However, in clinical practice a minimum clinically important change in IELT has not been defined. In the pooled analysis, the improvement in mean 12-week IELT from baseline for the placebo group was 1 minute and the difference between placebo and dapoxetine 30 mg for the improvement in mean 12-week IELT was 1.2 minutes. In both the pooled analysis and the individual studies, the difference between dapoxetine 30 mg and 60 mg 'on demand' for the mean IELT at 12 weeks was less than 1 minute.

- Very common (greater than 1 in 10 men) adverse reactions reported in the summary of product characteristics are dizziness, headache and nausea. Contraindications to the use of dapoxetine include significant pathological cardiac conditions such as heart failure, significant ischaemic heart disease or history of syncope; a history of mania or severe depression; moderate and severe hepatic impairment; and concomitant treatment with monoamine oxidase inhibitors, thioridazine, SSRIs, tricyclic antidepressants or other herbal/medicinal products with serotonergic effects and potent CYP3A4 inhibitors. The summary of product characteristics states that men should be advised not to use dapoxetine in combination with recreational drugs or alcohol. Treatment with dapoxetine should not be initiated with the 60 mg dose. If a man has an orthostatic reaction on the 30 mg dose, the dose should not be increased to 60 mg. For further information on contraindications, cautions and warnings please refer to the summary of product characteristics.

- There are no RCTs that compare 'on demand' dapoxetine with an active comparator such as daily use of a longer-acting SSRI (off-label use). In addition, there are limited data available on the safety and efficacy of dapoxetine 'on demand' for longer than 24 weeks. The studies only included men aged 18 years and over (the average age in the pooled analysis was 41 years) in a monogamous heterosexual relationship for at least 6 months who met DSM-IV-TR criteria for premature ejaculation. The efficacy and safety of dapoxetine have not been established in men aged 65 years and over.

Full text of Evidence review.

Context

The European Association of Urology 2014 guidelines on male sexual dysfunction recommend that non-pharmacological treatments for premature ejaculation which are beneficial include psychosexual counselling, education, and behavioural treatments. Pharmacological treatment options for premature ejaculation include 'on demand' dapoxetine, daily use of a longer-acting SSRI (off-label use), daily use of clomipramine (off-label use), 'on demand' topical local anaesthetic agents (off-label use) or 'on demand' tramadol (off-label use).

Full text of Context.

Estimated impact for the NHS

The European Association of Urology 2014 guidelines on male sexual dysfunction state that in men for whom premature ejaculation causes few if any problems treatment should be limited to psychosexual counselling and education. For a number of men, pharmacological treatment of premature ejaculation will not be acceptable. Various behavioural techniques have demonstrated benefit in treating premature ejaculation and are indicated for men uncomfortable with pharmacological therapy. In lifelong premature ejaculation (onset from the first sexual experience and remaining during life), the European guidelines state that behavioural techniques are not recommended for first-line treatment because they are time-intensive, require the support of a partner and can be difficult to do. Pharmacotherapy is recommended as first-line therapy.

The summary of product characteristics for dapoxetine states that a careful appraisal of the individual benefit/risk ratio should be carried out after the first 4 weeks of treatment (or at least after 6 doses of treatment) with dapoxetine to determine whether continuing

treatment is appropriate. If dapoxetine is continued the benefit/risk balance should be re-evaluated at least every 6 months.

Dapoxetine is the only medicine licensed in the UK for the treatment of premature ejaculation, although other treatments are used off-label for this indication. The General Medical Council advice to use a licensed medicine whenever possible should be taken into consideration.

Full text of Estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

The European Association of Urology 2014 guidelines on male sexual dysfunction state that although premature ejaculation is a very common male sexual dysfunction (with prevalence rates of 20% to 30%), its aetiology is poorly understood. In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), premature ejaculation is defined as '*persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity*'. The major point of debate between the DSM-IV-TR definition of premature ejaculation and other definitions is quantifying the time to ejaculation, which is usually described as the intravaginal ejaculatory latency time (IELT).

Premature ejaculation is classified as 'lifelong' (primary) or 'acquired' (secondary). Lifelong premature ejaculation is characterised by onset from the first sexual experience and

remaining during life with ejaculation occurring too fast (before vaginal penetration or less than 1 to 2 minutes after). Acquired premature ejaculation is characterised by a gradual or sudden onset - after previous normal ejaculation experiences; time to ejaculation is short but usually not as short as in lifelong premature ejaculation. The European guidelines recommend that the diagnosis and classification of premature ejaculation is based on medical and sexual history and that it should include assessment of IELT, perceived control, distress and interpersonal difficulty. It is important to distinguish premature ejaculation from erectile dysfunction. Erectile dysfunction or other sexual dysfunction or genitourinary infection (for example, prostatitis) should be treated first.

The European guidelines state that in men for whom premature ejaculation causes few if any problems treatment should be limited to psychosexual counselling and education. Before beginning treatment the guidelines recommend that it is essential to discuss expectations of treatment thoroughly. Various behavioural techniques have demonstrated benefit in treating premature ejaculation and are indicated for men uncomfortable with pharmacological therapy.

In lifelong premature ejaculation, the European guidelines state that pharmacological treatment should be the first-line option; behavioural techniques are not recommended as first-line treatment because they are time-intensive, require the support of a partner and can be difficult to do. The guidelines recommend that pharmacological treatment options include 'on demand' dapoxetine, daily use of a longer-acting selective serotonin reuptake inhibitor (off-label use), daily use of clomipramine (off-label use), 'on demand' use of topical local anaesthetic agents (off-label use), or 'on demand' tramadol (off-label use). Dapoxetine (Priligy) is the first pharmacological treatment to be licensed in the UK for the treatment of premature ejaculation.

Product overview

Drug action

Dapoxetine is a short-acting selective serotonin-reuptake inhibitor (SSRI). The time to maximum plasma concentration is about 1 to 2 hours after intake. Plasma levels are less than 5% of peak concentrations by 24 hours post-dose.

Human ejaculation is primarily mediated by the sympathetic nervous system. The mechanism of action of dapoxetine in premature ejaculation is presumed to be linked to

the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and postsynaptic receptors (Priligy summary of product characteristics).

Licensed therapeutic indication

Dapoxetine (Priligy) was launched in the UK in November 2013. It is licensed for the treatment of premature ejaculation in adult men aged 18 to 64 years. Dapoxetine should only be prescribed to men who meet all the following criteria:

- An intravaginal ejaculatory latency time of less than 2 minutes **and**
- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the man wishes **and**
- Marked personal distress or interpersonal difficulty as a consequence of premature ejaculation **and**
- Poor control over ejaculation **and**
- A history of premature ejaculation in the majority of intercourse attempts over the prior 6 months.

Dapoxetine should be administered only as on demand treatment before anticipated sexual activity. Dapoxetine should not be prescribed to delay ejaculation in men who have not been diagnosed with premature ejaculation.

Course and cost

Dapoxetine must not be taken more frequently than once every 24 hours (Priligy summary of product characteristics).

Dapoxetine is available at 2 different strengths: 30 mg and 60 mg. The recommended starting dose for all men is 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity. Treatment should not be initiated with the 60 mg dose. If the individual response to 30 mg is insufficient and the man has not experienced moderate or severe adverse reactions or prodromal symptoms suggestive of syncope, the dose may be increased to a maximum recommended dose of 60 mg taken as needed approximately 1 to 3 hours prior to sexual activity. The incidence and severity of adverse events is higher with the 60 mg dose.

The summary of product characteristics recommends that a careful appraisal of the individual benefit/risk ratio of dapoxetine should be performed by the clinician after the first 4 weeks of treatment (or at least after 6 doses of treatment) to determine whether continuing treatment is appropriate. Data regarding the efficacy and safety of dapoxetine beyond 24 weeks are limited. The clinical need of continuing and the benefit/risk balance of treatment should be re-evaluated at least every 6 months.

Dapoxetine (Priligy) is available in packs of 3 and 6 tablets. For the 30 mg strength tablet, the costs are £14.71 for a pack of 3 tablets and £26.48 for a pack of 6 tablets. For the 60 mg strength tablet, the costs are £19.12 for a pack of 3 tablets and £34.42 for a pack of 6 tablets (MIMS, March 2014).

Evidence review

This evidence summary is based on a pooled analysis of results from 5 phase III randomised controlled trials (RCTs) (McMahon et al. 2011). All 5 of the studies were conducted in heterosexual men aged 18 years and over who had been in a monogamous relationship for at least 6 months and who met the DSM-IV-TR criteria for premature ejaculation. In 4 of the studies, participants also had to have an intravaginal ejaculatory latency time (IELT) of 2 minutes or less in at least 75% of 4 or more sexual intercourse events at baseline. These 4 studies compared 'on demand' placebo, dapoxetine 30 mg and dapoxetine 60 mg over a 12- or 24-week period for the primary outcome of IELT, measured by a stopwatch held by the partner. The pooled analysis provides pooled data from these 4 studies for the mean average IELT at week 12. The 5th study compared dapoxetine 60 mg once daily, dapoxetine 60 mg 'on demand' and placebo over a 9-week period.

McMahon et al. (2011)

- Design: pooled analysis of 5 phase III RCTs: 2 identically designed 12-week randomised, double-blind, placebo-controlled, parallel group studies from the USA (Pryor et al. 2006); a 24-week randomised, double-blind, parallel group, placebo-controlled study primarily conducted in Europe and South America (Buvat et al. 2009); a 12-week randomised, double-blind, placebo-controlled, parallel group study in Asia-Pacific countries (McMahon et al. 2010); and a 9-week randomised, double-blind, placebo-controlled, parallel group study from North America (Kaufman et al. 2009).

- Population: the pooled analysis included 6081 men aged 18 years and over (mean age 41; 71% white) who had been in a monogamous heterosexual relationship for at least 6 months and who met DSM-IV-TR criteria for premature ejaculation. In 4 of the studies, participants also had to have an IELT of 2 minutes or less in at least 75% of 4 or more sexual intercourse events at baseline. Participants in the studies reported having premature ejaculation for an average of 15 years, with 65% of participants considered to have lifelong premature ejaculation by the study investigators. In those participants in whom it was recorded (n=4832), average IELT at baseline was 0.9 minutes.

- Intervention and comparison: in 4 studies (Pryor et al. 2006 [2 studies reported], Buvat et al. 2009 and McMahon et al. 2010) (n=4843), participants were randomised 1:1:1 to placebo, dapoxetine 30 mg or dapoxetine 60 mg to be taken 'on demand' (1 to 3 hours before anticipated sexual intercourse). In Kaufman et al. (2009) (n=1238), participants were randomised 2:2:1 to dapoxetine 60 mg once daily, dapoxetine 60 mg 'as needed' and placebo.

- Outcomes: 4 studies (Pryor et al. 2006, Buvat et al. 2009 and McMahon et al. 2010) evaluated IELT as the primary outcome, defined as the duration of time from penetration to intravaginal ejaculation and measured by a stopwatch held by the female partner during each episode of intercourse. The pooled analysis provides pooled data from these 4 studies for the mean average IELT at week 12. Secondary outcome measures in these 4 studies included patient-reported outcomes such as the clinical global impression of change in premature ejaculation (where participants were asked to rate their premature ejaculation as 'much worse', 'worse', 'slightly worse', 'no change', 'slightly better', 'better' or 'much better') and items from the Premature Ejaculation Profile (PEP), a validated tool that includes measures of perceived control over ejaculation. Missing post-baseline data were substituted with the last post-baseline observation carried forward. Three of the included studies (Pryor et al. 2006 and Kaufman et al. 2009) stated that participants were expected to attempt sexual intercourse 6 or more times each month during the study period. Safety outcomes included pooled data from all 5 studies for adverse events and safety observations of well-recognised selective serotonin reuptake inhibitor (SSRI)-related effects concerning mood, akathisia, anxiety, suicidality or SSRI discontinuation syndrome reported separately from each study.

Table 1 Summary ofpooled analysis McMahon et al. (2011)

	'on demand' placebo	'on demand' dapoxetine 30 mg	'on demand' dapoxetine 60 mg
Efficacy[a]	n=1612	n=1616	n=1615
Primary outcome: mean IELT in minutes (SD) at 12 weeks	baseline: 0.9 (0.48) (n=1608) 12 weeks: 1.9 (2.43) (n=1468)	baseline: 0.9 (0.49) (n=1613) 12 weeks: 3.1 (3.91) (n=1497) p<0.001 compared with placebo	baseline: 0.9 (0.49) (n=1611) 12 weeks: 3.6 (3.85) (n=1449) p<0.001 compared with placebo
Geometric mean IELT in minutes (SE) at 12 weeks	baseline: 0.8 (1.02) 12 weeks: 1.3 (1.02) (n=1455)	baseline: 0.8 (1.02) 12 weeks: 2.0 (1.03) (n=1486) p<0.001 compared with placebo	baseline: 0.8 (1.02) 12 weeks: 2.3 (1.03) (n=1437) p<0.001 compared with placebo
Selected secondary and additional outcomes:			
% of participants reporting 'good' or 'very good' perceived control over ejaculation	Baseline: 0.3% (n=1608) 12-weeks: 11.2% (n=1461)	Baseline: 0.6% (n=1614) 12 weeks: 26.2% (n=1489) p<0.001 compared with placebo	Baseline: 0.5% (n=1613) 12 weeks: 30.2% (n=1460) p<0.001 compared with placebo

% of participants reporting 'good' or 'very good' satisfaction with sexual intercourse	Baseline: 15.5% (n=1608) 12-weeks: 24.4% (n=1461)	Baseline: 14.7% (n=1614) 12-weeks: 37.9% (n=1489) p<0.001 compared with placebo	Baseline: 15.5% (n=1613) 12-weeks: 42.8% (n=1459) p<0.001 compared with placebo
% of participants reporting that their PE was 'better' or 'much better' at week 12	13.9% (n=1460)	30.7% (n=1487) p<0.001 compared with placebo	38.3% (n=1456) p<0.001 compared with placebo
Safety[b]	n=1857[c]	n=1616	n=2106
Participants reporting adverse events	651 (35.1%)	760 (47.0%)	1,270 (60.3%)
Participants with adverse events leading to discontinuation	1.0%	3.5%	8.8%
Participants reporting nausea	41 (2.2%)	178 (11.0%)	467 (22.2%)
Participants reporting dizziness	40 (2.2%)	94 (5.8%)	230 (10.9%)

Abbreviations: IELT, intravaginal ejaculatory latency time; n, number of participants; p, p value; SD, standard deviation; SE, standard error.

[a] The efficacy outcomes shown in the table are based on pooled analysis from 4 of the 5 phase III studies.

[b] The safety outcomes shown in the table are based on pooled analysis from the 5 phase III studies but do not include the dapoxetine 60 mg once daily group from Kaufman et al. (2009). No statistical analysis was presented for the safety outcomes.

[c] Also included here are the participants from the placebo arm of the Kaufman et al. (2009) study. These participants took placebo once daily and placebo 'on demand'.

Clinical effectiveness

The pooled analysis of results from 4 phase III studies showed that there was an increase

from baseline in mean IELT at 12 weeks with all 3 groups, including the placebo group. There was a statistically significantly greater increase from baseline in mean IELT at 12 weeks with both dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' (from 0.9 minutes in all groups to 1.9, 3.1 and 3.6 minutes respectively for placebo, dapoxetine 30 mg and dapoxetine 60 mg; $p<0.001$ for comparisons with placebo).

The RCTs that contributed to the pooled analysis also individually showed statistically significantly greater increases of similar magnitude in mean IELT at 12 weeks with both strengths of dapoxetine compared with placebo ($p<0.001$). One of the included studies (Buvat et al. 2009) was continued for 24 weeks and the statistically significant increase in mean IELT with dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' was still maintained at this time point ($p<0.001$).

McMahon et al. (2011) also presented exploratory analyses of geometric means (a measure of central tendency) for the 12-week IELT. Because IELT may be influenced by several factors and it is not expected to be normally distributed, it has been previously suggested that geometric mean may be preferred over average mean to correct for this skewed distribution. The increase from baseline in geometric mean values for IELT was also statistically significantly greater for dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' ($p<0.001$).

Whilst there is no generally agreed minimum clinically important change in IELT, Pryor et al. (2006) concluded that it was about 1 minute, based on a correlation of global impression of change scores with mean changes in IELT. In the pooled analysis, the improvement in mean 12-week IELT from baseline for the placebo group was 1 minute. In the pooled analysis, the difference between placebo and dapoxetine 30 mg for the improvement in mean 12-week IELT was 1.2 minutes. In both the pooled analysis and the individual studies, the difference between dapoxetine 30 mg and 60 mg 'on demand' for the mean IELT at 12 weeks was less than 1 minute (0.5 minutes for the pooled analysis; no statistical analysis reported).

The percentage of men who reported that their premature ejaculation was 'better' or 'much better', and who reported 'good' or 'very good' satisfaction with sexual intercourse and 'good' or 'very good' perceived control over ejaculation was statistically significantly higher with dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' (all $p<0.001$, see table 1 for details). However, the differences between the 30 mg and 60 mg strengths were small (no statistical analysis reported). In addition, the majority of

men in the dapoxetine groups (69.3% in the 30 mg group and 61.7% in the 60 mg group) did not report that their PE was 'better' or 'much better'.

McMahon et al. (2011) also presented pooled analyses from 2 of the included studies (Buvat et al. 2009 and McMahon et al. 2010) for the percentage of men reporting 'quite a bit' or 'extreme' ejaculation-related personal distress or ejaculation-related interpersonal difficulty. For both of these outcomes there were statistically significant reductions with dapoxetine 30 mg and 60 mg compared with placebo at 12 weeks. For the percentage of men reporting 'quite a bit' or 'extreme' ejaculation-related personal distress, there was a reduction from 73.5% (545/742) to 39.0% (268/688) with placebo, from 71.3% (529/742) to 28.2% (194/689) with dapoxetine 30 mg and from 69.7% (519/745) to 22.2% (153/690) with dapoxetine 60 mg ($p<0.001$ for comparisons with placebo). For the percentage of men reporting 'quite a bit' or 'extreme' ejaculation-related interpersonal difficulty, there was a reduction from 38.5% (286/742) to 23.8% (164/688) with placebo, from 38.8% (288/742) to 16.0% (110/689) with dapoxetine 30 mg and from 36.1% (269/745) to 12.3% (85/690) with dapoxetine 60 mg ($p<0.001$ for comparisons with placebo).

As part of the process of granting a UK marketing authorisation for dapoxetine, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) considered evidence on the benefit/risk balance of the 60 mg dose. Concerns had been raised that the benefit of 60 mg compared with 30 mg was considered too modest to outweigh the potentially increased risk for severe events of syncope. The CHMP concluded that a statistically significant efficacy difference in favour of 60 mg compared with 30 mg had been established. However, the mean (or median) difference in IELT between the 30 mg and 60 mg dose appears marginal. The CHMP concluded that based on IELT data as well as patient- and partner-reported outcome measures, at least 12% more men respond to dapoxetine 30 mg compared with placebo and an additional 5–10% more men respond to the 60 mg dose compared with the 30 mg dose. The CHMP also recommended that additional changes were to be made to the summary of product characteristics to further optimise the benefit-risk ratio (see Safety and tolerability section).

Safety and tolerability

In the pooled analysis (McMahon et al. 2011), adverse events occurred in 35.1% of men in the placebo groups, 47.0% in the dapoxetine 30 mg 'on demand' groups and 60.3% in the dapoxetine 60 mg 'on demand' groups. Across the groups approximately 3% of men reported severe adverse events and 1% or less of men reported serious adverse events.

Across all 5 RCTs, syncope (including loss of consciousness) occurred in 0.05% of men in the placebo groups, 0.06% of men in the dapoxetine 30 mg groups and 0.23% of men in the dapoxetine 60 mg groups (no statistical analysis presented).

Orthostatic hypotension has been reported in clinical trials, and the summary of product characteristics includes recommendations to minimise this risk. This states that before treatment initiation, a careful medical examination including history of orthostatic events should be performed by the clinician. An orthostatic test should be performed before initiating therapy (blood pressure and pulse rate, supine and standing). The man should be counselled on the risk of prodromal symptoms such as light-headedness soon after standing and the risk of syncope. Treatment with dapoxetine should not be initiated with the 60 mg dose, and if a man has an orthostatic reaction on the 30 mg dose, the dose should not be increased to 60 mg.

A 12-week open-label, prospective observational study (Mirone et al. 2014) assessed the safety profile of dapoxetine compared with 'alternative care'. A total of 9443 men (mean age 40 years) were assessed: 6128 were treated with dapoxetine 30 mg or 60 mg 'on demand' and 3315 were treated with 'alternative care'. In the alternative care group, men were treated in a variety of ways including oral treatment with longer-acting SSRIs such as paroxetine or sertraline, topical treatment or behavioural counselling. Treatment-emergent adverse events were reported by 12.0% of the dapoxetine group compared with 8.9% of the alternative care group. The most common treatment-emergent adverse events were nausea, headache and vertigo, with a higher incidence in the dapoxetine group (3.1%, 2.6% and 1.0% respectively) than in men who were taking oral treatment in the alternative care group (2.3%, 1.3% and 0.9% respectively). Men in the dapoxetine group had an orthostatic test at baseline: 70 men had an orthostatic reaction and 60 of these men took dapoxetine and were included in the safety analysis. No syncope events were reported in any of the men treated with dapoxetine during the study. However, the observational design of this study limits the conclusions that can be drawn.

As highlighted in the dapoxetine summary of product characteristics, antidepressants (including SSRIs) increased the risk of suicidal thinking and suicidality compared with placebo in short-term studies in children and young people with major depressive disorder and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults who are aged over 24. In the pooled analysis, it was reported that there was no evidence of men feeling suicidal whilst taking dapoxetine treatment (no statistical analysis presented). The mean age of the population in the pooled analysis was 41 years.

Analysis of data from Buvat et al. (2009) and Kaufman et al. (2009) found no effect on mood, or evidence of treatment-emergent anxiety or akathisia.

The summary of product characteristics states that contraindications to the use of dapoxetine include significant pathological cardiac conditions such as heart failure, significant ischaemic heart disease or history of syncope; a history of mania or severe depression; and concomitant treatment with thioridazine, monoamine oxidase inhibitors, SSRIs, tricyclic antidepressants or other herbal/medicinal products with serotonergic effects and potent CYP3A4 inhibitors. It also states that dapoxetine should not be used in men taking phosphodiesterase type 5 inhibitors (for example, sildenafil).

Dapoxetine should be used with caution in men with mild or moderate renal impairment, and is not recommended for use in men with severe renal impairment. It is contraindicated in men with moderate and severe hepatic impairment. The efficacy and safety of dapoxetine have not been established in men aged 65 years and over (summary of product characteristics).

Very common (greater than 1 in 10 men) adverse reactions reported in the summary of product characteristics are dizziness, headache and nausea. Common (between 1 in 100 and 1 in 10 men) adverse reactions reported include anxiety, agitation, insomnia, somnolence, abnormal dreams, tremor, paraesthesia, blurred vision, tinnitus, erectile dysfunction, decreased libido, increased blood pressure, hyperhidrosis and gastrointestinal disorders.

The summary of product characteristics states that patients should be advised not to use dapoxetine in combination with recreational drugs or alcohol.

Dapoxetine has a number of potential drug interactions; these are similar to those which occur with other SSRIs. For further information on contraindications, cautions and warnings please refer to the summary of product characteristics.

Evidence strengths and limitations

The pooled analysis included data from 6081 men and reported results for both IELT and patient-reported outcomes such as perceived control over ejaculation. However, there are no RCTs that compare 'on demand' dapoxetine with an active comparator, such as daily use of a longer-acting SSRI (off-label use).

The studies only included men aged 18 years and over who had been in a monogamous heterosexual relationship for at least 6 months and who met Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition, text revision (DSM-IV-TR) criteria for premature ejaculation. In 4 of the RCTs included in the pooled analysis, participants also had to have an intravaginal ejaculatory latency time of 2 minutes or less, and this is reflected in the licensed indication. Only 3 of the studies included in the pooled analysis stated how frequently men were to try to attempt sexual intercourse; the other 2 included studies did not state this. The average age of men in the pooled analysis was 41 years. The efficacy and safety of dapoxetine have not been established in men aged 65 years and over.

In 3 of the RCTs (Buvat et al. 2009 and Pryor et al. 2006) included in the pooled analysis, the method of allocation described suggests that this was concealed. However, in the other 2 RCTs (McMahon et al. 2010 and Kaufman et al. 2009) it is unclear if allocation was concealed. The efficacy outcomes were reported to be based on the intention-to-treat (ITT) population, classed as all randomised participants. However, in the pooled analysis, numbers of participants for whom data were available was also presented. It is unclear if the analysis was based on the ITT population or the population for whom data were available. Discontinuation rates were high in the studies but were similar for dapoxetine and placebo (31.1% of all participants in the dapoxetine groups and 28.9% of all participants in the placebo groups). For missing data post-baseline, the last post-baseline observation carried forward (LPOCF) method was used. In this approach, regardless of when a patient left the trial (for example, after week 1, week 6 or week 12), the last available result for that patient was carried forward and analysed as though it were the result at the study end.

As stated in the summary of product characteristics, the efficacy and safety of dapoxetine in men with both premature ejaculation and erectile dysfunction treated with both dapoxetine and phosphodiesterase type 5 inhibitors (for example, sildenafil) has not been established. The summary of product characteristics states that dapoxetine should not be used in men taking phosphodiesterase type 5 inhibitors.

There are limited data available on the safety and efficacy of dapoxetine 'on demand' for longer than 24 weeks.

Context

Alternative treatments

The European Association of Urology 2014 guidelines on male sexual dysfunction recommend that pharmacological treatment options include 'on demand' dapoxetine, daily use of a longer-acting selective serotonin reuptake inhibitor (SSRI) [off-label use], daily use of clomipramine (off-label use), 'on demand' topical local anaesthetic agents (off-label use) and 'on demand' tramadol (off-label use). Because longer-acting SSRIs such as citalopram, fluoxetine or paroxetine have a longer onset of action than the shorter-acting dapoxetine they need to be taken on a daily basis and cannot be used as an 'on demand' treatment.

Costs of alternative treatments

	Estimated cost per 30 days treatment (excluding VAT)[a]
Citalopram 20 mg to 40 mg per day (off-label use)	£0.94 to £1.06
Fluoxetine 20 mg to 60 mg per day (off-label use)	£0.99 to £2.97 (based on using 3×20 mg capsules for a 60 mg dose)
Sertraline 25 mg to 200 mg per day (off-label use)	£1.12 to £6.38
Paroxetine 20 mg to 40 mg per day (off-label use)	£1.58 to £3.16
Clomipramine 25 mg to 50 mg per day (off-label use)	£1.66 to £1.99
Dapoxetine 30 mg 'on demand'	£14.71 for a 3-tablet pack and £26.48 for a 6-tablet pack
Dapoxetine 60 mg 'on demand'	£19.12 for a 3-tablet pack and £34.42 for a 6-tablet pack
Tramadol 'on demand' (off-label use)	£0.03 per 50 mg capsule
Topical local anaesthetic agents (off-label use) for example lidocaine 2.5% and prilocaine 2.5% cream	£2.25 for a 5 gram tube

[a] Prices based on Drug Tariff April 2014 and MIMS April 2014. Costs for off-label SSRIs are expressed as cost for 30 days of treatment based on usual doses for other conditions (see summaries of product characteristics for details). The cost of 30 days of treatment for dapoxetine will vary depending on the dose of dapoxetine and the quantity of tablets supplied each month. The same will apply to the off-label use of tramadol and the off-label use of topical local anaesthetic agents.

Estimated impact for the NHS

Likely place in therapy

The European Association of Urology 2014 guidelines on male sexual dysfunction states that in men for whom premature ejaculation causes few if any problems treatment should be limited to psychosexual counselling and education. The guidelines recommend that before beginning treatment, it is essential to discuss the expectations of treatment thoroughly. Various behavioural techniques have demonstrated benefit in treating premature ejaculation and are indicated for men who are uncomfortable with pharmacological therapy. In lifelong premature ejaculation, the European guidelines state that behavioural techniques are not recommended for first-line treatment because they are time-intensive, require the support of a partner and can be difficult to do.

The guidelines recommend that pharmacological treatment options include 'on demand' dapoxetine and daily use of a longer-acting SSRI such as citalopram, fluoxetine or paroxetine (off-label use) or daily use of clomipramine (off-label use). Dapoxetine is taken 'on demand' approximately 1 to 3 hours before anticipated sexual activity. This may reduce the incidence of SSRI-related adverse effects compared with the off-label use of once-daily longer acting SSRIs, although there are no direct RCTs to provide evidence for this. However, some men may prefer to take a daily dose which may allow more spontaneity than a planned 'on demand' treatment.

Dapoxetine is licensed for treating premature ejaculation in adult men aged 18 to 64 years. The summary of product characteristics states that dapoxetine should only be prescribed to men who meet all the following criteria:

- An intravaginal ejaculatory latency time of less than 2 minutes **and**

- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the man wishes **and**
- Marked personal distress or interpersonal difficulty as a consequence of premature ejaculation **and**
- Poor control over ejaculation **and**
- A history of premature ejaculation in the majority of intercourse attempts over the prior 6 months.

Dapoxetine should not be prescribed to delay ejaculation in men who have not been diagnosed with premature ejaculation. Therefore, men will need to be appropriately assessed and given a diagnosis of premature ejaculation in line with the above criteria before dapoxetine can be considered. In addition, the summary of product characteristics states that a careful appraisal of the individual benefit/risk ratio should be carried out after the first 4 weeks of treatment (or at least after 6 doses of treatment) to determine whether continuing treatment is appropriate. If dapoxetine is continued, the benefit/risk balance should be re-evaluated at least every 6 months. Consideration will need to be given to how treatment efficacy can be assessed given the subjective nature of efficacy outcomes.

Premature ejaculation can occur in conjunction with erectile dysfunction and the European Association of Urology 2014 guidelines on male sexual dysfunction states that if premature ejaculation is secondary to erectile dysfunction then the erectile dysfunction should be treated before or at the same time as the premature ejaculation. It should be noted however, that the summary of product characteristics states that dapoxetine should not be used in men taking phosphodiesterase type 5 inhibitors (for example, sildenafil) as this increases the risk of syncope.

For a number of men pharmacological treatment of premature ejaculation will not be acceptable. A prospective observational study from a single clinical centre in Italy (Mondaini et al. 2013) assessed the acceptance and discontinuation rates of 'on demand' dapoxetine 30 mg (titrated to 60 mg after 3 months if low efficacy) in 120 men with lifelong premature ejaculation. Twenty-four (20%) of the men decided not to start dapoxetine. Fear of using a 'drug' was the most frequently reported reason for treatment non-acceptance (50%). In addition, the majority of men who took dapoxetine discontinued treatment. The main reasons for treatment discontinuation were efficacy below expectations, side effects and costs. Out of the 96 men who decided to start dapoxetine, only 10 men were continuing the treatment after 1 year.

Dapoxetine is the only medicine licensed in the UK for the treatment of premature ejaculation, although other treatments are used off-label for this indication. The General Medical Council advice to use a licensed medicine whenever possible should be taken into consideration.

Estimated usage

The manufacturer has estimated that based on a GP-registered population of 100,000 people, 5851 men aged 18 to 64 will be affected by premature ejaculation with 1151 men severely affected (A. Menarini Farmaceutica Internazionale: personal communication January 2014).

The manufacturer further estimates that 25% of the men severely affected by premature ejaculation will seek treatment and 70% of those seeking treatment could be prescribed dapoxetine. The manufacturer therefore estimates that based on a GP-registered population of 100,000, 202 men aged 18 to 64 may potentially be prescribed dapoxetine over a 5-year period (A. Menarini Farmaceutica Internazionale: personal communication January 2014).

The manufacturer estimated that in 2013 approximately 75% of European sales of dapoxetine were for the 30 mg strength.

Relevance to NICE guidance programmes

Dapoxetine for premature ejaculation was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

There is no NICE guidance on premature ejaculation.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

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