New Medicine Assessment

Dapoxetine (Priligy®▼)

Treatment of premature ejaculation (PE) in men 18 to 64 years of age

Recommendation: Rag Status BLACK

Dapoxetine (Priligy) is not recommended for the treatment of PE.

Compared with placebo, dapoxetine statistically significantly increased the intravaginal ejaculation latency time. However, when trialled against an active comparator (off label use of an SSRI) a treatment benefit has not been consistently demonstrated. Evidence of clinical benefit to justify the significantly higher treatment costs is uncertain.

Summary of supporting evidence.

- Dapoxetine is the only oral licensed product available for the treatment of PE and is the only short acting SSRI on the market allowing for "on demand" use.
- Five phase 3 placebo controlled trials have consistently shown a statistically significant increase in intravaginal ejaculation latency time (IELT) with dapoxetine 30mg and 60mg on demand from a baseline of 0.9 – 1.1 minutes to 2.8 – 4.2 minutes compared to placebo 0.9 – 1.0 minute to 1.8 - 2.4 minutes.
- Significant improvements in PE compared with placebo were also accompanied by improvements in patient reported outcomes.
- A 1 month active comparator study of on demand dapoxetine versus daily paroxetine 20mg showed a similar increase in intravaginal ejaculation latency time (IELT) between dapoxetine 30 mg and paroxetine of 117% (53.2 and 54.1 seconds respectively). A significantly greater increase in IELT was demonstrated for dapoxetine 60 mg on demand of 170% (74.7 seconds).
- A 12 week active comparator study demonstrated an increase in IELT of 371% (141 seconds) for dapoxetine 60mg daily in contrast to a 1094% (339 second) increase for paroxetine 20mg daily and a 62% (21 second) increase for placebo.
- The difference in results from the two active comparator studies could be explained by the difference in duration of the studies and the different dosing schedule for dapoxetine (daily versus on demand).
- The cost of dapoxetine, used 3-6 times a month, is significantly higher than that of other SSRIs used off label
- Dapoxetine was generally well tolerated. The most common treatment emergent adverse events (TEAEs) reported were nausea and dizziness. 30 cases of syncope were observed during the clinical trials, but only half were considered as medically confirmed and all occurred before implementation of activities (administration of patient instructions and titration of doses) intended to minimise the occurrence of syncope.

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- Men with concomitant erectile dysfunction were excluded in the dapoxetine trials, for this reason the use of dapoxetine in patients with concomitant erectile dysfunction is not supported
- In being the only short acting SSRI available it may be preferred by some patients not wishing to take an SSRI continuously, conversely, some men may prefer the alternative option of off-label SSRIs daily allowing more spontaneity than a planned “on demand” treatment.

Details of Review

Name of medicine (generic & brand name)**:**
Dapoxetine (Priligy®)

Strength(s) and form(s):
Film-coated tablets, 30mg and 60mg[1]

Dose and administration:
Starting dose of 30mg taken 1-3 hours prior to sexual activity. Not to be repeated within 24 hours. If ineffective and patient does not experience side effects the dose may be increased to 60mg.

BNF therapeutic class / mode of action
Chapter 4.3.3 / SSRI – a potent selective serotonin re-uptake inhibitor
Chapter 7.4 Other urologicals

Licensed indication(s):
Treatment of premature ejaculation (PE) in men 18 to 64 years of age

Proposed use (if different from, or in addition to, licensed indication above):
Only to be prescribed when patient meets the following criteria

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

Course and cost:

Based on "PRN" use of 6 tablets per month[2]

Dapoxetine 30mg £26.48, annual costs £317.76

Dapoxetine 60mg £34.42, annual costs £413.04

Current standard of care/comparator therapies:[3]

Off label SSRIs and TCAs taken daily, PDE5 inhibitors on demand in conjunction with SSRI (When PE co-exists with ED), and tramadol.

Off label use of topical lidocaine/ prilocaine

Behavioural psychotherapy to manage the anxiety (not found to be effective alone for PE)

Relevant NICE guidance:

Dapoxetine for premature ejaculation was not considered appropriate for a NICE technology appraisal[4] and is not currently planned into any other work programme. There is no NICE guidance on premature ejaculation.

Background and context

Premature ejaculation (PE) is the most common male sexual dysfunction. The prevalence of PE is not related to age but varies according to definition and methodology for collecting data. A Cochrane review quoted a prevalence range of 3-30%[5], while the European Association of Urology reports a prevalence of 20-30%[6].

PE can be differentiated into lifelong or acquired PE. Lifelong PE is characterised by onset from the first sexual experience, remains so during life and can be defined as "A male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy".[3] Acquired PE is secondary to other conditions and has been associated with chronic proctitis and specific endocrinopathies, including diabetes mellitus and hyperthyroidism. In these instances, PE is usually reversed when the underlying disorder is treated.[7] It can be gradual or sudden onset following normal ejaculation experiences before onset and time to ejaculation is short but not usually as short as lifelong PE.[6]

The male sexual response comprises four phases: excitement, including erection; plateau; ejaculation, usually accompanied by orgasm; and resolution.

Ejaculation is a complex response involving a sequential process requiring co-ordination between sympathetic, parasympathetic and somatic efferent pathways originating from different segments and area in the spinal cord. Excitatory and inhibitory influences from sensory genital and cerebral stimuli are integrated and processed in the spinal cord. Ejaculatory latency of less than 1 minute, inability to delay ejaculation and negative personal consequences all define this dysfunction. The neurotransmitters which mediate the ejaculation process involve serotonin and serotonergic pathways, dopaminergic and oxytocinergic systems. Dapoxetine targets the serotonergic pathways.

Serotonin activity delays ejaculation and it has been observed that a side effect of selective serotonin reuptake inhibitor antidepressants (SSRI's) is a delay in ejaculation. The 2014 European Association of Urology guidelines on male sexual dysfunction[6] state that SSRIs are the first choice treatment in lifelong PE. Dapoxetine is the only on-demand pharmacological treatment approved for PE in European countries. Daily treatment with fluoxetine, sertraline and paroxetine is off-label and has the risk of withdrawal if suddenly stopped. All other medications used in PE are off-label indications such as clomipramine (a tricyclic antidepressant) and on-demand topical anaesthetic agents which are the oldest pharmacological therapy and is a viable alternative to SSRIs, have consistently shown efficacy in PE. Long-term outcomes for pharmacological treatments are unknown[8].

Dapoxetine is a more potent SSRI and is the first to be licensed for the treatment of PE in men aged 18 – 64 years of age. It is more rapidly eliminated than other SSRIs which allows for "on-demand" use and is not intended for continuous daily use[1].

Dapoxetine has been available since April 2010 on private prescription through Lloyds Pharmacy which sells Priligy[9] exclusively online in the UK, following an online consultation, at a cost of £76 for three 30mg tabs. However in November 2013 it became prescribable on the NHS.[10]

Summary of evidence

Summary of efficacy data in proposed use:

The efficacy of dapoxetine 30mg and 60mg was evaluated in four[11] randomised, double-blind, placebo-controlled phase III studies over 12-24 weeks (see table for summary) with a total of 4844 men enrolled. An additional study[11, 12] over 9 weeks looked at dapoxetine 60mg prn and daily against placebo with 1238 men enrolled. The diagnostic criteria for PE was defined as onset of orgasm and ejaculation with minimal sexual stimulation on or shortly after penetration and before the person wished, in most episodes of intercourse within the 6 months prior to enrolment. This in addition to marked distress or interpersonal difficulties due to PE. The men were enrolled if they were in a stable monogamous, heterosexual relationship for ≥ 6 months and had an intravaginal ejaculatory latency time (IELT) of ≤ 2 minutes in at least 75% of the time. Exclusion criteria were concomitant use of SSRIs or tricyclic antidepressants, major psychiatric disorders, history of medical illness, uncontrolled hypertension, erectile and other forms of sexual dysfunction. The 12 and 24 week studies evaluated IELT as the primary outcome which was measured by a stopwatch held by the female partner during each episode of intercourse. Secondary outcome measures included patient-reported outcomes such as the clinical global impression of change in PE (rated as "much worse", "worse", "slightly worse", "slightly better", "better" or "much better") and measures of perceived control over ejaculation included in a validated tool Premature Ejaculation Profile (PEP).

Study NCT00229073[13] – 24 weeks of treatment with placebo (n=385), dapoxetine 30mg (n=388) or 60mg (n=389), 53% of participants completed the study. The primary endpoint of mean IELT at week 24 resulted in a significant increase from baseline (0.9 minutes) with dapoxetine 30mg to 3.1 minutes and with 60mg to 3.5 minutes compared with placebo to 1.9 minutes, p<0.001 for both doses.

Study NCT00210704[14] – 12 weeks of treatment with placebo (n=357), dapoxetine 30mg (n=354) or 60mg (n=356), 80% of participants completed the study. The primary endpoint of mean IELT at week 12 resulted in a significant increase with dapoxetine 30mg to 3.9 minutes and with 60mg to 4.2 minutes from baseline (1.1 minutes) compared with placebo to 2.4 minutes from baseline (1.0 minute), p<0.001 for both doses.

Study NCT00211107 & NCT00211094 (integrated analysis)[15] – 12 weeks of treatment with placebo (n=870), dapoxetine 30mg (n=874) or 60mg (n=870), 75% of participants completed the study. The primary endpoint of mean IELT at week 12 resulted in a significant increase from baseline (0.9 minutes for all treatment groups) with dapoxetine 30mg to 2.8 minutes and with 60mg to 3.3 minutes compared with placebo to 1.8 minutes, p<0.0001 for both doses. Studies NCT00211107 and NCT00211094 were combined for an integrated analysis which went on to enrol the subjects into a multicentre, open-label, 9-month extension study[11], the results of the extension study are not available for inclusion in this evidence review.

Study NCT00210613[12] - 9 weeks of treatment with placebo (n=245), dapoxetine 60mg prn (n=491) or 60mg daily (n=502) had 66% completing the study. The primary endpoints were patient reported outcomes of perceived control over ejaculation (P=1.6, D=2.1), personal distress related to ejaculation (P=2.0, D=1.5), interpersonal difficulty related to ejaculation (P=1.1, D=0.8) and satisfaction with sexual intercourse (P=2.0, D=2.5), p<0.001 for all reported outcomes favouring dapoxetine.

Studies were consistent and showed that dapoxetine 30mg and 60mg prn significantly prolonged IELT and improved all patient reported outcomes (PROs) compared with placebo in men with PE at 12 weeks. One of the studies showed that the statistically significant increase in mean IELT

with dapoxetine 30mg and 60mg compared with placebo was still maintained at 24 weeks, ($p<0.001$).

A prospective observational study from a single centre in Italy[4,17] presented at a conference suggested that 20% of patients declined to opt for oral dapoxetine when offered the treatment (a quarter of these were due to costs of treatment) and after one year 90% of those having started treatment had discontinued, again a quarter of these were due to costs. The main reasons for discontinuation were side effects, lack of efficacy or efficacy below expectations. If supplied on prescription (FP10) in the UK, drug costs would not present such a significant issue.

Direct comparator evidence against SSRIs is limited to two studies. The first study compared the use of dapoxetine with daily paroxetine.[20] This one month study divided patients into three groups of 50 men; group 1 received on-demand dapoxetine 30 mg, group 2 on-demand dapoxetine 60 mg and group 3 were treated with daily paroxetine 20 mg. Patients were included if they were in a stable relationship for at least 6 months and had an IELT of less than 1 minute.
All three groups saw a significant increase in IELT from baseline, with paroxetine 20 mg and dapoxetine 30 mg giving similar increases of 117% or 53.2 ($p<0.01$) and 54.1 ($p<0.01$) seconds respectively: dapoxetine 60 mg saw a 170% increase in IELT or 74.7 ($p<0.01$) second improvement.

This result is in contrast to the second comparator study, published in 2006 and available as an abstract only,[21] this 12 week study compared dapoxetine 60 mg (n=115), paroxetine 20 mg (n=113) and placebo (n=112) all taken on a daily rather than on-demand basis. IELT increased from a baseline of 38, 31 and 34 seconds to 179, 370 and 55 seconds respectively; showing a far greater increase for paroxetine over the dapoxetine. This study also measured mean intercourse satisfaction domain values of International Index of Erectile Function (IIEF) these increased from a baseline of 10, 11 and 11 for dapoxetine, paroxetine and placebo to 14, 17 and 12 at the end of the 12 weeks for the three groups respectively[21]: this again favours the paroxetine.

The difference in results for the two active comparator studies could be partially explained by the daily rather than on-demand use of dapoxetine in the 12 week study and the short duration of the 1 month study. Dapoxetine has maximum plasma concentration 1-2 hours post dose, a terminal half-life of 19 hours and plasma levels 5% of peak 24 hours post dose. SSRIs need be given for 1 to 2 weeks to be effective in PE1 so the SSRI may not have been exhibiting its full therapeutic effect at the end of the 1 month study.

Before dapoxetine on demand was available, daily treatment with SSRIs was the first choice treatment in PE[6]. A systematic review and meta-analysis of all drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE[19].

In the meta-analysis studies subject to greater variability were removed leaving 8 prospective, double-blind, real time stopwatch studies. In these studies SSRIs increased the geometric mean IELT by 295% to 783%. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline[19].

Summary of safety data:

In five studies a total of 4224 men were treated with active drug.[8] 1616 took dapoxetine 30mg as needed and 2608 took dapoxetine 60mg either as needed or continuously once a day. The most common side effects were headache, dizziness and nausea reported ≥ 1 in 10 patients. Medicine related syncope has been reported in the clinical trials but in most cases occurring within the first 3 hours after doses. In the combined analysis of two trials (study NCT00229073 and study NCT00210613) syncope was reported in two patients taking placebo and nine patients taking dapoxetine (less than 1%).

In the Study NCT00210613[8,12,16] of the 5 patients who reported syncope during the study, 3 experienced a loss of consciousness. These adverse events of syncope occurred after administration of the first dose of dapoxetine at the study site on Day 1 and appeared to have a vasovagal aetiology.

In total, 30 cases of syncope[11] were observed during the clinical trials, but only half were considered as medically confirmed and all occurred before implementation of activities (administration of patient instructions and titration of doses) intended to minimise the occurrence of syncope. Post-authorisation, there were nine events reported, four of these events are associated with 30mg dose and five with the 60mg dose but not all were confirmed medically. Nausea and dizziness were the main adverse events leading to discontinuation (2.5% and 1% respectively). Overall discontinuation rates in the studies ranged from 2-4% with 30mg, 5-10% with 60mg and ≤1% taking placebo.

One of these studies of 9 weeks[16] duration looked specifically at withdrawal effects of dapoxetine 60mg prn and 60mg once daily. Results on the primary endpoint measurement based on weekly Discontinuation-Emergent Signs & Symptoms (DESS) produced no evidence of a withdrawal effect of dapoxetine 60mg when abruptly discontinued. However, the slightly higher incidence of mild and moderate insomnia and dizziness in subjects to placebo after receiving dapoxetine 60mg daily for 62 days compared with continuous dapoxetine 60mg daily suggests that the occurrence of mild withdrawal symptoms cannot be excluded.

Strengths and limitations of the evidence:

Strengths:

- Consistent results across several studies
- Large number of participants in studies (n=6081)
- Two out of the five trials are based on patient orientated outcomes as the primary endpoint
- Three of the five studies described the method of allocation suggesting that it was concealed. It is unclear whether allocation was concealed in the other two studies.

Limitations:

- The study populations were limited to those with IELT consistently ≤ 2 minutes and with PE described as moderate to severe, therefore these results cannot be generalised to milder forms of PE.
- Treatment benefit against active comparators including off label daily treatment with SSRIs has not been consistently demonstrated.
- Men with concomitant erectile dysfunction were excluded in the dapoxetine trials, for this reason the use of dapoxetine in patients with concomitant erectile dysfunction is not supported
- PE not defined as either lifelong or acquired in the studies

- Trials were not designed to compare the two doses of dapoxetine
- Limited evidence of safety beyond 24 weeks
- High rate of discontinuation, possibly due to intrusive nature of endpoint assessment

Summary of evidence on cost effectiveness:

No published evidence on the cost effectiveness of Priligy® in the UK has been identified. There are no published active-comparator trials for the use of Priligy®.

Prescribing and risk management issues:

Priligy® is contraindicated[1] in:

- Hypersensitivity to the active substance or to any of the excipients
- In patients with significant pathological heart conditions e.g. heart failure (NYHA class II-IV), conduction abnormalities such as AV block or sick sinus syndrome, significant ischaemic heart disease, significant valvular disease and a history of syncope
- A history of mania, hypomania, bipolar disorder or severe depression
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), thioridazine, SSRIs, SNRIs, TCAs, tramadol, linezolid, lithium, St John's Wort. With all of these drugs it is important to remember that a wash out period is required either before or after treatment with Priligy®.
- Concomitant treatment with potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazadone, nelfinavir, azatanavir
- Patients prescribed PDE5 inhibitors for erectile dysfunction
- In combination with either alcohol or recreational drugs
- In severe renal impairment
- Unstable epilepsy
- Hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption

Caution is advised in:

- Co-prescribing of medicinal products with vasodilation properties e.g. alpha adrenergic receptor agonists and nitrates
- Co-prescribing with moderate CYP3A4 inhibitors e.g. erythromycin, clarithromycin, verapamil or diltiazem. Dose should be restricted to 30mg.
- Due to potential for SSRIs to lower the seizure threshold, patients with controlled epilepsy should be carefully monitored
- Concomitant prescribing of medicines which affect platelet function – risk of haemorrhage
- Patients with raised intra-ocular pressure or those at risk of angle closure glaucoma
- Patients with mild to moderate renal impairment

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year (ex VAT)
Dapoxetine 30mg	1 prn, up to 6 per month	£26.48	£317.76
Dapoxetine 60mg	1 prn, up to 6 per month	£34.42	£413.04
Fluoxetine 20mg	1 od	£1.02	£13.26
Sertraline 50mg	1 od	£6.35	£82.55
Paroxetine 20mg	1 od	£1.63	£21.19
Tramadol 50mg	1 prn	£1.09	£14.17
Lidocaine/ prilocaine cream 5g	Apply prn	£2.25	£29.25
Costs based on MIMS list prices March 2014[2] This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

No additional monitoring costs are anticipated with the use of Priligy and no discounts are available

Productivity, service delivery, implementation:

The information provided by Menarini Farmaceutica Internationzionale[18] in the budget impact template postulates that compared with current practice, the public recognition of a condition and the availability of a licenced treatment may increase the numbers of patients presenting each year and hence being referred to secondary care for assessment in outpatient clinics with subsequent costs:

Budget impact: Outpatient referrals			
	Current situation	Potential future situation	
		With diagnosis and treatment for suitable patients in primary care	Without diagnosis and treatment for suitable patients in primary care
Men affected by PE/ 100,000 of the population	5,851	5,851	5,851
Proportion of these presenting each year	3.2%	19.2%	19.2%
Proportion of these referred to secondary care	30%	8%	50%
Number of referrals to secondary care	56	90	562
Cost per attendance at hospital outpatient clinic	£129	£129	£129
Overall cost of referrals	£7,245	£11,592	£72,453

As these figures are based on a population of 100,000 and the total population across Lancashire is 1.5million these figures need to be multiplied 15-fold to reflect possible costs in Lancashire which would then range from £173,880 to £1,086,795.

Anticipated patient numbers and net budget impact:

There are 528,516 men aged between 18 and 64 across Lancashire. A Cochrane review quoted a prevalence range of 3-30%, while the European Association of Urology reports a prevalence of 20-30%.

Data for prevalence provided by the manufacturer estimates that 18.8% of men will be affected by premature ejaculation, this equates to 99,361 men in Lancashire. The manufacturer further estimates that 19.7% of patients with PE are considered to be severe but that only 25% of these patients are likely to present to the GP.

Based on the assumption above it can be estimated that there would be 4,894 patients presenting to their GP with PE which they considered to be severe across Lancashire, assuming that 70% of patients who present to their GP are likely to be prescribed dapoxetine and based on the dosing assumptions in Appendix A the total annual cost to treat all patients in Lancashire would be £819,061.

The company model further estimates that 20% of eligible patients will be initiated each year with a dropout rate of 40% per year, this estimates that costs would start at £98,229 in the first year rising to £491,384 in year 5.

Innovation, need, equity:

SSRIs are currently used off-label to improve PE but need to be taken daily to be effective. Whereas dapoxetine has rapid onset and quick elimination therefore making it more suited to "on-demand" use. There is no other drug with this specific action and **therefore would meet the criteria for innovation**. However some men may prefer to take a daily dose which may allow more spontaneity than a planned "on demand" treatment.

As there are treatment guidelines for life-long and acquired PE that include pharmacological interventions for both, all of which are unlicensed or off-label, the availability of a licensed drug **fulfils an unmet pharmaceutical need**.

With improved knowledge and acceptance of this condition there would be an increase in numbers wishing to be treated and equitable access would be needed for patients with either lifelong or acquired PE. However treatment should be in conjunction with behavioural psychotherapy and equitable access to this support would also be required.

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Table: Summary of key Dapoxetine RCTs relevant to use in Premature Ejaculation

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Study NCT00229073 [8,13]						
1	Double-blind, randomised, placebo-controlled 24 week study	Men >18yrs in stable monogamous relationship for ≥6mths who met criteria for PE for >6mths, indicated moderate PE-related distress or interpersonal difficulty and reported IELT of <2mins in 75% of evaluable events during 4wk screening period. N=1162	Dapoxetine 30mg (n=388) and 60mg (n=389) prn vs placebo (n=385) Study medication taken 1-3hrs before anticipated sexual intercourse. Review every 4 wks AEs actively solicited at each visit. 53% completed the study	Change from baseline of average IELT measured using a stopwatch by participant/partners (To detect a 1-min difference in mean IELT between placebo and dapoxetine 60mg) IELT baseline for all patients 0.9minutes IELT endpoint: Placebo = 1.9mins D30mg = 3.1 mins (p<0.001) D60mg = 3.5 mins (p<0.001) Proposed 1 minute difference between placebo and dapoxetine 60mg met	Compared to the start of the study, the clinical global impression (CGI) of change in PE rating of "better" or "much better": Placebo = 54/347 (15.6%) D30mg = 110/359 (30.6%), p<0.001 D60mg = 138/352 (39.2%), p<0.001	Primary outcome is DOO. Level 3 evidence based on primary outcome is DOO 1:1:1 using computer-generated randomisation schedule (interactive voice response system) Double blinded Intention to treat analysis 90% power for sample size of 258 per treatment group but did not achieve target enrolment of 1300 to account for rate of dropout of 40% Risk of bias: less than 80% completed the study
Study NCT00210704 [8,14]						
2	Double-blind, randomised, placebo-controlled, parallel-group 12 week study	Men ≥18yrs in stable monogamous relationship for ≥6mths and planned to maintain relationship, who met criteria for PE for >6mths, indicated moderate PE-related distress or interpersonal difficulty and reported IELT of <2mins in 75% of evaluable events during 4wk screening period. N= 1067 600 patients to be Asian	Dapoxetine 30mg (n=354) and 60mg (n=356) prn vs placebo (n=385) Study medication taken 1-3hrs before anticipated sexual intercourse. Review every 4 wks AEs actively solicited at each visit. 80% completed the study	Change from baseline of average IELT measured using a stopwatch by female partner and PROs IELT baseline 1.0, 1.1 and 1.1minutes respectively IELT endpoint: Placebo = 2.4mins D30mg = 3.9 mins (p<0.001) D60mg = 4.2 mins (p<0.001) PRO measures of "good" or "very good" at baseline 1.6, 0.9 and 0.6% respectively PRO at 4 weeks and maintained to 12 weeks: Placebo = 18.7%	Compared to the start of the study, the clinical global impression (CGI) of change in PE rating of "better": Placebo = 75 (22%) D30mg = 123 (37.4%), p<0.001 D60mg = 140 (41.5%), p<0.001	Primary outcome is DOO & POO. Level 2 evidence based on POOs but does not meet level 1 criteria 1:1:1 allocation method not specified Double blinded Intention to treat analysis Power or sample size not stated 80%completed the study

				D30mg = 33.5% (p<0.001) D60mg = 33.5% (p<0.001)		
Study NCT00211107 and NCT00211094 [8,15]						
3	Double-blind, randomised, placebo-controlled, parallel-group 12 week study	Men ≥ 18 yrs in stable monogamous relationship for ≥ 6mths and planned to maintain relationship, who met criteria for PE for > 6mths, indicated severe PE-related distress or interpersonal difficulty IELT of "before, upon, shortly after penetration or before the person wished" in most SI episodes N=2614	Dapoxetine 30mg (n=429) and 60mg (n=425) prn vs placebo (n=440) with attempted SI six or more times per month	Change from baseline of average IELT measured using a stopwatch by female partner at week 12 or final visit. IELT endpoint for all pts: Placebo = 1.8mins D30mg = 2.8 mins D60mg = 3.3 mins 75% completed the study	Secondary endpoints included male and female self-reporting of PE profile: vital signs and adverse events were recorded at week 4 and 12 or final visit. Compared to the start of the study, the patient global impression of change in PE rating of "fair, good, very good": Placebo = 200 (26%) D30mg = 467 (58%), p<0.001 vs placebo D60mg = 515 (67%), p<0.001 vs placebo 1% discontinued due to lack of efficacy	Primary outcome is DOO. Level 3 evidence based on primary outcome is DOO 1:1:1 using computer-generated randomisation schedule (interactive voice response system) 98% power for sample size of 300 per treatment group met with all except those stratified to <30sec IELT Risk of bias: less than 80% completed the study
4	Double-blind, randomised, placebo-controlled, parallel-group 12 week study		Dapoxetine 30mg (n=445) and 60mg (n=445) prn vs placebo (n=430) with attempted SI six or more times per month			
Study NCT00210613 [8,12,16]						
5	Double-blind, double-dummy, randomised, placebo-controlled, parallel-group 9 week study	Men ≥ 18 yrs in stable monogamous relationship for≥ 6mths and planned to maintain relationship, who met criteria for PE for >6mths, indicated moderate PE-related distress or interpersonal difficulty IELT of "before, upon or shortly after penetration" N=1238	Dapoxetine 60mg prn (n=491) and 60mg daily (n=502) vs placebo (n=245) Study medication taken 1-3hrs before anticipated sexual intercourse and daily. AEs actively solicited at each visit. (Treatment phase followed by withdrawal assessment and follow up – see below)	PRO at week 9 (mean score) Control: placebo = 1.6, D60 = 2.1 (p<0.001) Distress: placebo = 2.0, D60 = 1.5 (p<0.001) Interpersonal: placebo = 1.1, D60 = 0.8 (p<0.001) Satisfaction: placebo = 2;.0, D60 = 2.5 (p<0.001) 811 (66%) completed the study	Extent of therapeutic response Adverse events reporting >5%	Primary outcome is POO Risk of bias: less than 80% completed the study
6	Double-blind, double-dummy, second randomisation follow-on withdrawal 4 week study	As above. N=811	At Day 63 of above trial, patients were randomised to either their previous treatment or placebo for 7 days. Follow up visit after 7 days. Post-study telephone contact 14 days after discontinuation of study drug.	Withdrawal effects measured by DESS checklist weekly 8 had discontinuation syndrome: D60 daily/placebo = 2(1.3%)	Assess new and existing adverse events 5 patients reported syncope, 3 of which lost consciousness for 15 seconds to 1 minute 1 patient reported suicidal ideation	Primary outcome is patient-reported outcome measures (POO) Allocation method not specified Double blinded

				D60 daily/D60 daily = 1 (0.6%) D60 prn/placebo = 1 (0.7%) D60 prn/D60 prn = 2 (1.4%) Placebo/placebo = 2 (1.3%)	1 patient reported abnormal dream AEs reported in 2% of subjects during withdrawal period: diarrhoea, headache, insomnia, nausea, irritability and dizziness. Slightly higher incidence of mild or moderate insomnia and dizziness in subjects switched to placebo from daily D60 suggests occurrence of mild withdrawal effects.	ITT and MITT % completing study not reported Level 2 evidence based on POOs but does not meet level 1 criteria Risk of bias: unknown % completed the study
Footnotes: PE= premature ejaculation; IELT = intravaginal ejaculation latency time; PEP = Premature Ejaculation Profile ; PRO = patient reported outcomes; DESS = Discontinuation-Emergent Signs & Symptoms; AE = adverse events; POO = patient orientated outcomes; DOO = disease orientated outcomes; ITT = intention to treat; MITT = modified intention to treat; SI = sexual intercourse						

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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Appendix A

Budget Impact Model for Dapoxetine

(Population figures derived from a NICE costing template to identify latest local demographics rather than use of a national average model 100,000 patients)

CCG	Pop >18yrs	Pop >65yrs	Difference	% males	Target pop	18.8%* of men 18-64 yrs have PE	19.7% of PE is severe	25% of severe PE will present to GP
Blackburn	127304	12444	114860	50.6	58119	10926	2153	538
Blackbpool	139464	18296	121168	50.6	61311	11526	2271	568
C&SR	138815	16611	122204	49.5	60491	11372	2240	560
East Lancs	288262	33187	255075	49.9	127282	23929	4714	1179
F & W	124265	20496	103769	48.3	50120	9423	1856	464
GP	168546	17625	150921	50.6	76366	14357	2828	707
Lancs North	129910	15964	113946	49.8	56745	10668	2102	525
West Lancs	89196	11478	77718	49	38082	7159	1410	353
	1205762	146101	1059661			99361	19574	4894

Assumption: 70% who present are likely to be prescribed Priligy **3426**

Worse case scenario 100% take up no drop outs
Assume dosage split 75% take 30mg and 25% take 60mg
Assume quantity/mth split 60% on 3 tabs and 40% on 6 tabs
(Annual cost 3 x 30mg = £158.88; 3 x 60mg = 206.52)

	30mg	60mg
	2570	856
3 tabs	£244,993	£106,151
6 tabs	£326,657	£141,260
	£571,650	£247,411

Total annual cost: £ 819,061

Budget impact calculation over 5 years based on 3,426 men likley to be treated with Priligy
Assumption: 20% of patients treated per year, cumulative total. At the same time 40% drop out rate
Assumption: cost per patient per year based on an average cost of the above calculation = £239

Year	% uptake	Number of patients	40% drop out	Patients who carry on	GP costs per annum
1	20	685	274	411	£98,229
2	40	1370	548	822	£196,458
3	60	2056	822	1234	£294,926
4	80	2741	1096	1645	£393,155
5	100	3426	1370	2056	£491,384

*Personal communication from Menarini Farmaceutica Internationzionale