

# SUBMISSION FOR RECLASSIFICATION OF SILDENAFIL TABLETS

## EXECUTIVE SUMMARY

This application requests consideration of the reclassification of sildenafil under strict criteria for availability through especially trained pharmacists.

Availability of sildenafil is not a new initiative, being available under patient group direction (PGD) in the United Kingdom (UK) since 2007.[1] Furthermore, reclassification has been mooted in the UK by Kelly,[2] and Aronson,[3] and also in Japan by independent academics concerned at the excessive supplies with no health professional involvement.[4]

Sildenafil is a well-characterised medicine, prescribed to over 37 million men with well over a billion tablets dispensed as at 2008.[5] The medicine is well-tolerated with a substantial safety margin.[5, 6] Adverse events tend to be transient and mild to moderate. Sildenafil has few contraindications.[6]

We have taken a careful and comprehensive approach to this reclassification to provide an environment in which sildenafil can be supplied appropriately. Pharmacists will be especially trained, a screening tool will be used, and strict criteria for supply will be set. With this reclassification, pharmacists will take a further step up to provide significant benefits to consumers with a condition affecting both their quality of life and relationships. Furthermore, pharmacists will be providing early cardiovascular screening to those who may not otherwise be screened for a considerable time, and will be strongly recommending the consumer advise his doctor of this common complaint if not already done so. There is no doubt that this will identify people who need treatment earlier than would otherwise occur.

We have been more conservative than the UK PGD supplies, in order to maximise the benefits to consumers and minimise risks. We have used input from practicing community pharmacists, a general practitioner with an interest in men's sexual health and a cardiologist to develop our screening tool and training outline.

New Zealand (NZ) community pharmacists have embraced recent initiatives and taken such responsibilities seriously, for example with oseltamivir, trimethoprim, vaccinations and warfarin management. This has been supported by research for oseltamivir[7, 8] and warfarin,[9] and anecdotal feedback on other medicines. Pharmacists are well-trained health professionals who are welcoming the opportunity to work at the top of their scopes of practice. Additional to patient benefits, these initiatives are contributing to increased job satisfaction and interest in stepping up even further as health professionals contributing to good patient health.

Erectile dysfunction (ED) impacts quality of life,[10] being associated with depression, anxiety and low self-esteem,[11-13] and affecting a sufferer's relationship with his partner.[14] Sildenafil provides benefits in these areas,[13-18] and treatment with phosphodiesterase 5 inhibitors (PDE-5Is) is recommended first-line for ED.[10] However, only 10% of doctors routinely ask about ED for patients with chronic conditions, and only a fifth of men with ED discuss it with their doctor.[12] Diabetic men are even less likely to discuss it with their doctor. Men typically delay their presentation to their doctor with ED, often for years,[19] or seek medicine from internet sites to avoid the doctor.[4, 20]

Men in NZ (like other countries) access doctors less frequently than women, with many barriers to their visits including opening hours that do not fit their timing and lack of knowledge of risk factors.[21] The extended hours of pharmacy, informal environment, and ability to walk in without an appointment may encourage men to visit early for a resolution to their ED, allowing an opportunity to screen and recommend a full check-up at

the doctors. In the UK, the PGD has enabled such screening which has resulted in men being referred on and treated for hypertension.

Our sildenafil supply with extensive screening will help to address an unmet need in men's health in NZ, encouraging appropriate access to a registered product and enabling an early discussion of a condition that can be very embarrassing, but also can indicate other health problems.

## PART A

**1. International non-proprietary name (or British approved name, or US adopted name) of the medicine**

Sildenafil

**2. Proprietary name (s)**

The product marketed by Douglas Pharmaceuticals is Silvasta®.

Other products with consent to distribute in NZ containing sildenafil are: Avigra®; Silagra®; Vedafile®; and Viagra®.

**3. Name of company/organisation/individual requesting reclassification**

Douglas Pharmaceuticals Limited

**4. Dose form(s) and strength(s) for which a change is sought**

Tablets up to 100 mg.

**5. Pack size and other qualifications**

The proposed pack size is 4. It is proposed that up to 8 tablets could be supplied at a time. This is sufficient to allow adequate trial, patient convenience and minimisation of embarrassment, and is smaller than UK patient group directions (PGDs; see Appendix 1)

**6. Indications for which change is sought**

Erectile dysfunction in adult males.

**7. Present classification of medicine**

Prescription only medicine

**8. Classification sought**

Pharmacist-only medicine when supplied in the approved pack, according to the approved requirements for supply, to a male aged 35-70 years, presenting in the pharmacy in person, by a pharmacist who has passed the approved training programme and is accredited to supply sildenafil.

Note: Training is mandatory. See Appendix 2 for information about the training and requirements for supply. The training will have independent over-sight from a pharmacy academic, and includes input from a doctor with expertise in this field, a cardiologist, psychologists, and a pharmacy academic. A screening form will be used at least annually (Appendix 3), with checks at each supply of changes in health and medication.

Note: the requirements of the Pharmacy Council Protocol for the Sale and Supply of Pharmacist Only Medicines for Chronic conditions (Appendix 4) will also apply. This protocol includes:

- Face-to-face consultations whenever possible unless due to disability or geographical isolation within NZ this is impractical
- No sale to patients who reside outside of NZ unless a face-to-face consultation occurs
- A requirement to exercise professional judgement to prevent the supply of medicines that are unnecessary or in excess to the patient's needs
- Electronic record of the sale of the medicine as for a prescription medicine, including directions for use

- Follow-up information is collected and added to the patient's record
- Other health practitioners caring for the patient are referred to or consulted with if necessary and with the patient's permission

**9. Classification status in other countries (especially Australia, UK, USA, Canada)**

Sildenafil is a prescription medicine in other countries.

In the UK, sildenafil has been supplied on PGDs since 2007.[22, 23] PGDs require that the pharmacist conforms to certain requirements in supplying the medicine. See attached papers and documents (Appendix 1). The proposed NZ supply is similar in that there are certain requirements for medicines supply. However, the reclassification model is more conservative than the UK supply, with a higher minimum age of 35 in our proposal (versus 18 years old in one PGD), a lower maximum age of 70 years (versus 75 years in one PGD), CV screening, and consideration of other potential causes of ED.

The primary reason why sildenafil has not been reclassified in the UK appears to be because of the European Medicines Agency (EMA) requirement that medicines registered centrally in Europe need to be reclassified centrally (i.e. for all 27 member states in one application).[2] As Portugal no longer has a pharmacist-only or pharmacy-only category of medicine supply,[24] this would allow sales in any outlet in that country, which raises concerns for the committee considering a European reclassification.[25] In contrast, provision through pharmacists in NZ provides mandatory health professional involvement. Furthermore, pharmacists would be subject to minimum requirements including training (outlined in Appendix 2) and full screening of patients for supply annually, and abbreviated screening at each visit (Appendix 3).

**10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute**

IMS sales data show 191,500 packs of sildenafil-containing medicines sold in the 12 months to May 2013. Based on an average use of two packs per year per man, this suggests the NZ market includes about 95,000 men getting sildenafil.

According to the Medsafe website, sildenafil was first registered in NZ on the 29<sup>th</sup> of October 1998.

By 2008, sildenafil had been prescribed to more than 37 million men worldwide and over a billion tablets had been dispensed.[5] Five years on, these numbers can only have increased further. Additionally, illegal use internationally, e.g. via the internet, will include counterfeit products, so international exposure to sildenafil will be considerably higher than the figures provided. NZ exposure may also be higher, with anecdotal reports of consumers purchasing the medicine when travelling (e.g. to Fiji) and bringing it home, and illicit supplies including from the internet.

**11. Labelling or draft labeling for the proposed new presentation(s)**

See Appendix 5 for the draft labelling and pack insert.

**12. Proposed warning statements if applicable**

Do not give this medicine to anyone else.

Some people should not take Silvasta - tell your pharmacist or doctor of your other medicines or medical conditions. Some heart medicines and other medicines must **not** be taken with Silvasta (e.g.

angina/chest pain medicines, amyl nitrate 'poppers', other medicines for erections; see pack insert). Do not take Silvasta if you have been advised to avoid vigorous exercise.

**13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.**

Other brands of sildenafil marketed in NZ include Avigra, Silagra, Vedafile and Viagra. Other brands having Consent to Distribute are listed as "not available" on the Medsafe website.

## PART B

### 1. A statement of the benefits to both the consumer and to the public expected from the proposed change

A 2013 review in the Lancet stated:[26]

*“... erectile dysfunction is now regarded as a major health problem for the increasingly healthy ageing population.”*

Benefits of reclassification are as follows:

1. Providing a first-line treatment to men with a clinical need, resolving that need and increasing their quality of life and their relationship
2. Encouraging men to discuss ED with a health professional early
3. Providing cardiovascular (CV) screening to men with a warning sign of a potential problem, resulting in a triage of men who may not be seeing their doctor
4. Encouraging men to get a regular doctor check-up and to discuss their ED with their doctor (through the pharmacist’s suggestion)
5. Potentially reducing the illicit supply of ED drugs, including internet supply, some of which will include counterfeits, or supplements with undeclared medicine
6. Having pharmacists trained in CV screening and comfortable with undertaking CV risk conversations in their pharmacies
7. Prompting discussions on smoking cessation and other health measures as identified in screening
8. Having pharmacists working at the top of their scopes of practice, as recommended by Health Workforce NZ for health professionals,[27] increasing pharmacists’ job satisfaction and their capability

Erectile dysfunction (ED), *“the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance,”*[10] is a common and distressing condition for many men. For many men PDE5 inhibitors provide an effective treatment, including in men with diabetes, depression and prostate cancer. PDE5 inhibitors are the first-line treatment for ED.[10, 19]

#### *Quality of life*

ED considerably impacts quality of life.[10] ED affects the sexual life of a sufferer and his partner (and their relationship),[14] and is associated with depression, anxiety and low self-esteem.[11] In diabetic men also, ED increases depression, and reduces self-esteem, self-confidence and quality of life.[12] Emotional disturbances provoked by ED contribute to compliance issues in diabetes. For example, 43% of men who stop taking their diabetes medication (including insulin) do it hoping to resolve their ED problems.[12] By including this type of information in the training for pharmacists and encouraging them to open up these sorts of conversations, patient education opportunities may be encouraged, and compliance issues may be better managed for the patient.

Men with untreated ED rate significantly lower on self-esteem, relationships and confidence than men without ED.[13] Treatment with sildenafil resolves this discrepancy.[13-18] Improvements in self-esteem correlate strongly with improvements in erectile function score.[28] An observational study in primary care mimicking real-life and using the LISAT 8 questionnaire, found sildenafil in men with ED significantly improved satisfaction in general life, family life, relationship with partner and sex life, with the latter two effects especially strong.[29] Patients with depression had significantly greater increase in satisfaction in general life and family life compared to other subgroups. Partner

respondents were mostly satisfied or very satisfied with treatments and 95% wanted their partner to continue sildenafil for ED. Other studies of PDE5-inhibitors have also found good rates of partner satisfaction.[30, 31]

The American Heart Association Guidelines report that:[32]

*“Changes in sexual activity after a cardiac event may impair the patient’s quality of life, negatively affect psychological health, and strain marital or other important intimate relationships, which in turn may lead to depression and anxiety. The resultant depression may be an important contributing cause of ED in men...”*

While men with a heart attack would be excluded from OTC treatment, this quote illustrates the important impact of ED on a sufferer’s life.

#### *Prevalence and doctor contact*

The prevalence of ED is 1-10% in men under 40 years, 2-15% for 40-50, and increases with age, to 20-40% in men 60-69, and well over 50% in men over 70 years.[33] Variability occurs because of sampling and questioning. In diabetic men, ED occurs 4.5 times more frequently than in non-diabetics, and starts 10-15 years earlier.[12] However, only 10% of doctors routinely ask about ED for patients with chronic conditions (partly owing to lack of time), and only a fifth of men with ED discuss it with their doctor, with even fewer diabetics with ED raising the subject with their doctor. Reluctance for men with diabetes stems from not wanting to put their doctor in an awkward situation or because they are unaware that ED can be treated. Doctors frequently do not recommend a prescription first-line,[12] despite the first-line therapy being lifestyle and risk factor modification and PDE-5 inhibitors.[10]

Men typically delay their presentation to their doctor with ED, often for years,[19] or seek medicine from internet sites to avoid the doctor.[4, 20] In trials ED had been present on average for 4.5 years before entering the trial.[5] Unfortunately, long-standing ED can be more difficult to treat because sexual behavior has been long modified by anxiety.[12] We want to encourage early identification to provide greater success in treatment as well as allow early screening.

Furthermore, we note an inequality between men and women in accessing health in NZ (and internationally).[21] NZ men experience barriers to health service utilization, with Māori and Asian males particularly reticent about accessing healthcare. Reasons why men find it difficult to engage with health services could include: lack of knowledge of services or of risk factors; lack of motivation or stoic predispositions; inappropriate opening times of services; inappropriate targeting of interventions or insufficient available services; or perception that health services are not ‘male-friendly’.[21] Possible solutions for NZ men mooted by Johnson et al include providing services at ‘work-friendly’ hours; setting up health checks targeting at-risk men, and use of wider community initiatives.[21] We would add to this a ‘drop-in’ service which does not require an appointment. Sildenafil in pharmacy overcomes some of these barriers. Opening hours are extended, no appointment is required, and a request in pharmacy for sildenafil may highlight at-risk men, allowing early screening and raising awareness of the importance of regular visits to the GP.

#### *Causative factors and screening*

Predisposing factors to ED include hypertension, atherosclerosis, hyperlipidaemia, cigarette smoking and diabetes mellitus.[32] The penile artery has a smaller diameter than coronary arteries, and therefore an atherosclerotic plaque in the smaller arteries could provide symptoms (i.e. ED) earlier than angina would be triggered in wider coronary arteries. Successful management of these conditions will typically help ED, thus, early presentation of ED patients is important to allow the

opportunity for early lifestyle advice, early referral to the doctor and encouragement of adherence to treatments for these conditions. ED presence strongly predicts CVD, particularly in men under 60 years,[26] and therefore reclassification of sildenafil is likely to encourage an earlier screening for CVD than would otherwise occur. The health benefits of identifying men in their 40s and 50s at risk of coronary events, screening and referring to the doctor could be large, particularly given this population group may not be regularly visiting their doctor, and NZ's Best Practice Advisory Centre (BPAC) reports ED is "*often present for many years before a man presents to his GP*".[19] Lifestyle advice that has been proven to help ED, i.e. achieving a normal weight, managing lipids, stopping smoking and increasing physical activity, will be counselled by the pharmacist and will be mentioned in the pack insert (Appendix 4). Resolving ED is a useful incentive to encourage changes in behaviour.

#### *Depression*

Depression can cause ED,[19] and ED can contribute to depression.[32] Currently these people may not be discussing this with their doctor and therefore the potential for pharmacists to raise this issue could provide earlier GP consultation about depression than might otherwise occur. See also Further Information at the end of the application.

#### *Identifying medicines that cause ED*

A variety of medicines can cause ED.[26] While this will not be the primary cause of most ED seen, identifying ED concerns relating to these medicines could minimize the risk of the patient discontinuing their medication without discussing with the prescriber. The training will include medicines causing ED and managing this issue.

#### *Illegal supply*

A further benefit relates to illegal supply. Aronson,[3] Kelly[2] and Sugita and Miyakawa[4] all believe that widening access through pharmacy would help to reduce the illicit supply of medicines that may be counterfeit and are supplied without health professional consultation. One 2012 study found 77% of internet-acquired sildenafil is counterfeit,[34] and in Europe, an estimated 44% of internet-supplied sildenafil is counterfeit.[35] Counterfeit drugs may contain unknown quantities of the labelled drug (from 0% to more than the labelled strength) or may contain other drugs. One hundred and fifty hospitalisations and four deaths were reported in Singapore in 2008 following counterfeit hypoglycaemia-tainted ED drugs[4] and a further similar death in Singapore was reported in 2012.[36] Friend-acquired 'Cialis' (containing glibenclamide) caused severe hypoglycaemia requiring hospitalisation in a man in Australia.[37]

In Japan, it has been estimated that the counterfeit market for PDE-5 inhibitors is 2.5 times that of the genuine products, driven by consumer convenience through avoidance of doctor consultation.[4] Consumers do not realize these are counterfeit, partly because they are sold at a similar price to the genuine article to reduce the consumer's suspicion. Sugita and Miyakawa in 2010 (independent academics with no funding from the drug companies) recommended that this counterfeit supply in Japan be addressed by physicians warning of the health dangers of internet supply and by shifting these medicines to non-prescription availability.[4] Users of counterfeit drugs are reluctant to report adverse effects, so the risk is likely to be considerably higher than represented here.[4] In Europe, PDE-5Is are the most commonly counterfeited medicine, with 36 million counterfeit sildenafil tablets seized from 2004-2008.[35] Some products contain other ingredients as well, including hypoglycaemics, naproxen, lidocaine, chloramphenicol,[38] and amphetamine.[35] Three internet-based studies have found 25-32% of men getting PDE-5Is have done so outside of the healthcare system (e.g. internet, friend).[35, 39] Reasons given for internet sourcing included pricing, and embarrassment to speak to the doctor.[39]



In the US, the Food and Drug Administration (FDA) has named more than 330 dietary supplements adulterated with pharmaceuticals, of which sexual performance supplements are a significant proportion, with commentators recently calling the volume of sales of such products “staggering”.<sup>[38]</sup> One US manufacturer produced over one million capsules per month for three years. To decrease the use of sexual enhancement supplements, Cohen and Venhuis recommended “having a low threshold for prescribing PDE-5Is ... so that physicians can ensure that patients receive high-quality products and are counseled appropriately before their use.” In NZ, the proposed pharmacist-only availability would assist in the same way.

In the UK, Kelly lamented the requirement for the centralised European reclassification of medicines which precluded the possibility of reclassifying sildenafil in the UK alone.<sup>[2]</sup> A reclassification should have “legitimised the supply route, legitimised the condition and its treatment and brought the opportunity for health education”. OTC sildenafil is unlikely to increase illicit supplies, but may encourage legitimate use for those who want easier access than arranging an appointment with the doctor, or being reluctant to raise the issue with their doctor. Such cases would benefit from screening and counselling that would not otherwise occur, and have certainty of getting the labelled medication.

In NZ, postal packages are x-rayed and prescription medicines are only released on presentation by the end-user of a doctor’s prescription which occurs for about a quarter of all prescription medicine interceptions.<sup>[40]</sup> PDE-5Is are commonly intercepted, including counterfeit products.<sup>[41]</sup> However, the Director-General of Health warned in 2008 that not all imports may be able to be intercepted.<sup>[41]</sup> This warning was reiterated in 2010,<sup>[40]</sup> and has been confirmed by anecdote from three NZ purchasers of PED-5Is from the internet who reported a minority of their parcels being detained. Research has identified counterfeit PDE-5Is entering NZ containing guano (bat and bird droppings), heavy metals including arsenic and mercury, different drugs (including a hypoglycaemic) or different strengths to that stated on the packet.<sup>[40]</sup> Furthermore, remedies containing undeclared PDE-5Is have been available for sale in NZ e.g. through adult shops, herbal stores, and even sometimes pharmacies until being identified and removed from the market.<sup>[42, 43]</sup> Additionally, a source reported friends who regularly purchased PDE-5Is in Fiji without prescription and brought them back into NZ for personal use. Likewise, travelers to the US or elsewhere could pick up an adulterated sexual performance supplement and miss any recall information on returning to NZ.

## **2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated**

Men know if they have difficulty with erections. However, a pharmacist will screen them to ensure they actually have erectile dysfunction, and to look for underlying causes such as heart disease that require referral. See the screening tool, Appendix 3. As in the UK PGD case study (Appendix 6), it is unlikely that a recreational user will want to undergo a 30 minute screening to get this medicine when other routes of supply may be easier.

Pharmacists will be trained in asking appropriate questions, including through filmed role plays of dummy consultations, and clips from experts discussing the condition and communication strategies.

## **3. Relevant comparative data for like compounds**

PDE-5Is are recommended first-line treatments for erectile dysfunction.<sup>[10, 19]</sup> Other recommended treatment options are not available without prescription. These include intracavernosal alprostadil

injections and testosterone. These two medicines are less commonly used than PDE-5 inhibitors. Penile prostheses are a further option but not usually recommended.

Herbal ingredients are available to support men’s sexual health, e.g. horny goat’s weed. Animal studies suggest these have some activity in ED.[44, 45] Panax ginseng (Korean ginseng) has shown a benefit on ED in human studies, although such studies apparently lacked robustness.[46] Icariin (in horny goat weed) has been shown to inhibit PDE-5, but a 2011 review noted no human studies had been conducted.[46] Multiple products are available containing these ingredients from NZ-based online suppliers (at least 10 NZ sites), health food shops, and some pharmacies. Online suppliers have up to four products each. A selection of such products is presented in Table 1.

**TABLE 1 EXAMPLES OF SUPPLEMENTS ON THE NZ MARKET TO SUPPORT MEN'S SEXUAL HEALTH**

| Product                            | What it does  | Ingredients  |
|------------------------------------|---|--|
| Go Healthy Go Man Plus             | “Go Man Plus is designed to enhance sexual energy, supporting a healthy libido, improving stamina and energy in times of need. Horny Goat Weed is well known for supporting healthy sexual function. Benefits: powerful sexual enhancer, supports healthy testosterone production.”   | Horny Goat Weed, Muira Puama, Damiana, Ginkgo biloba Tribulus, Korean Ginseng, Saw Palmetto, Deer Velvet, L-Arginine   |
| Xcitement Plus                     | One on-line site says: “Xcitement Plus may be just what you need to revitalise your sex life if you suffer from low libido, poor sexual stamina or performance, fatigue, lethargy, inability to perform in the bedroom, lack of sexual desire. Aphrodisiac, Increases Sex Drive, Boost Energy, Contains Horny Goat Weed and Tribulus.<br>If you are looking for a "natural Viagra like action" we would suggest trying this product instead UltraV and UltraV Economy Pack” | Tribulus Terrestris, Horny Goat Weed, Dulacia inopiflora, Avena sativa (oats), Panax Ginseng, Zinc   |
| Radiance Man Power                 | One on-line site says: “Tonic to men’s reproductive system. May help increase libido and performance. May also assist with stamina and increased energy levels”   | Horny goat weed, muira puama, maca root, tribulus, panax ginseng, damiana, ginkgo biloba, cayenne  |
| Pro Life Excite 4 Him              | One on-line site says: “These potent ingredients are beneficial for enhancing energy & stamina, stimulating circulation and assisting circulation and assisting sexual function.”   | Horny goat weed, muira Puama, maca root, tribulus, panax ginseng, damiana, ginkgo biloba, cayenne  |
| Nutralife Herbal Y Extreme for Men | “Helps enhance libido, stamina and sexual performance.<br>Helps increase peripheral circulation to the extremities.<br>Helps to tone the genito-urinary tract and enhance stamina.<br>Adaptogenic benefits of Ginseng help provide anti-stress effects and build stamina.”  | Horny goat weed, siberian ginseng, korean ginseng, small leafed willow, damiana, sarsaparilla, cayenne, winter cherry, tribulus terrestris, saw palmetto, ginkgo biloba, vitamin E, zinc, nicotinic acid |

Products containing undeclared PDE-5Is have been found on the market in NZ.[42] This includes remedies containing undeclared medicinal ingredients sold through retailers including adult sex shops and over the internet.

Thus, products are already on the market effectively for ED, providing an opportunity for consumers to self-medicate without screening. Illicit supply of PDE-5Is (e.g. over the internet) is considered later in this application.

#### **4. Local data or special considerations relating to New Zealand**

Data from NZ has been presented throughout this application where available, e.g. in partner satisfaction,[47, 48] reasons for discontinuing PDE-5Is,[31] men's delayed access to health,[21] and illicit supply.[40, 42]

#### **5. Interactions with other medicines**

The frequency and significance of interactions are similar to other non-prescription medicines. For example, aspirin and ibuprofen, available in the supermarket, are contraindicated with warfarin, and have a number of other precautions e.g. use with ACE inhibitors and diuretics, or with other anti-inflammatory medicines.

The most significant interaction is with nitrates, which are contraindicated owing to potential for additive hypotensive effects which can be unpredictable.[32] In the Pfizer clinical trials database only 16 men took nitrates with sildenafil and none reported hypotension. The post-marketing safety database included 478 reports of concomitant nitrate use, 11% of which reported hypotensive events.[5] However, such hypotensive events have the potential to be significant and must be avoided. Pharmacists already have high awareness of this interaction, but it will also be covered clearly in the training. This warning will be clearly marked on the pack and in the pack insert (Appendix 4), the screening will include names and photographs of the various nitrate products, and the counselling will specifically address this point (see Appendix 3). Dispensing history will be available if the person is at their usual pharmacy.

As sildenafil is a cytochrome P450 3A4 substrate, inhibitors of CYP3A4 may decrease metabolism of sildenafil and therefore increase its blood levels and duration in the body.[6] Conversely, inducers of CYP3A4 may reduce the blood levels and therefore effect of sildenafil.

Indiana University Drug Interaction charts show that strong inhibitors of CYP3A4 are indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, ketoconazole, and nefazodone.[49] Erythromycin is a weaker CYP3A4 inhibitor. The HIV drug, ritonavir is a highly potent inhibitor requiring considerable sildenafil dose reduction if used (maximum 25 mg per 48 hours).[6] We will be advising pharmacists to screen for these medicines, referring men taking ritonavir and other HIV protease inhibitors, and lowering the dose of sildenafil with erythromycin, ketoconazole and itraconazole. See the datasheet (Appendix 7) and the screening tool (Appendix 3) for more details.

Alpha-blockers with sildenafil may cause symptomatic hypotension in susceptible people.[6] Three studies with sildenafil (25-100 mg daily for two weeks) in stabilised doxazosin users found mean additional reductions in supine BP of 7/7 mmHg (25 mg dose), 9/5 mmHg (50 mg dose) and 8/4 mmHg (100 mg dose)[5] and infrequent reports of symptomatic postural hypotension with no cases

of fainting.[6] Spontaneous reports of problems with concomitant alpha-blockers were uncommon and most commonly unrelated to additive hypotensive effects.[5] Alpha-blockers will be screened for, and sildenafil only used in those who are stable on the alpha-blocker, the sildenafil dose is halved, and the patient advised to lie down if feeling dizzy. This is consistent with the use in the PGDs from the UK (Appendix 1).

Use with anti-hypertensives may cause small additive reductions in BP, but adverse cardiac events[32] and side effects in general[6] are not increased. Men taking more than two antihypertensives will be identified in screening. This reduces the risk of use in someone with more significant CV risk, and additive hypotension.

Use with other ED drugs may increase visual effects or adverse effects on the penis (e.g. priapism). Giuliano, et al. considered the safety risk of concomitant ED drugs was “likely to be low in the general ED population”. [5] However, given the potential for increased risk and datasheet recommendations, pharmacists will be screening for concomitant ED drugs and warning against use, supported by the pack insert.

## 6. Contraindications and precautions

Contraindications[6] and their management are covered in Table 2, and precautions[6] and their proposed management are covered in Table 3, or under interactions, above.

TABLE 2 CONTRAINDICATIONS AND THEIR PROPOSED MANAGEMENT

| Contraindication  | Management   |
|---|--|
| Hypersensitivity  | In screening   |
| Nitrate use (additive hypotensive effect)   | Screening for this (including with pictures)<br>Included in pack insert<br>Pack explains important interactions and to tell the pharmacist or doctor if taking any medicines |
| Where CV risk factors make sexual intercourse inadvisable, e.g. established cardiac failure, unstable angina pectoris | Screening for established cardiac disease and risk factors   |
| History of non-arteritic anterior ischaemic optic neuropathy  | Screened for previous eye problems   |
| Severe hepatic impairment   | Screened for liver problems  |
| Hypotension (BP <90/50 mmHg)  | BP measured annually or after relevant medication changes; a more conservative cut-off is used   |
| Hypertension (BP >170/110 mmHg)   | BP measured annually or after relevant medication changes; a more conservative cut-off is used   |
| Recent history of stroke or myocardial infarction (MI) and known hereditary retinal disorders                         | Included in screening  |

**TABLE 3 PRECAUTIONS AND THEIR PROPOSED MANAGEMENT**

| <b>Precautions</b>  | <b>Management</b>  |
|---|--|
| Sudden loss of vision in one or both eyes requires stopping treatment and seeking immediate medical attention   | This is a very rare effect and causality is uncertain<br>Screening for history of eye problems<br>Advice regarding eye problems in information sheet<br>Sudden loss of vision would likely be seen by consumers to be highly unusual and needing immediate medical treatment |
| Important CV risk e.g. recent onset angina, owing to CV risk associated with sexual intercourse   | Screening will result in doctor referral with a high safety margin, e.g. any angina would be reason for doctor referral.   |
| A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes and identify appropriate treatment | See the screening tool which has been developed with input from a cardiologist and general practitioner with extensive experience in men's sexual health   |
| Left ventricular outflow obstruction e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy  | Screening will include heart problems  |
| Anatomical deformation e.g. Peyronie's disease  | Asked about deformation  |
| Sickle cell anaemia, multiple myeloma, leukaemia owing to predisposing to priapism  | Screened for   |
| Prolonged erections (more than four hours, priapism) may occur and needs attention  | Included in pharmacist's advice and information sheet  |
| Transient visual disturbances and dizziness may affect driving  | Included in pharmacy advice and information sheet  |
| Dosing above 100 mg increases risk of adverse events  | A starting dose of 50 mg will be used as per the datasheet. Patients will be advised not to exceed the recommended dose. If they do, they are unlikely to get better benefit and may just feel unwell, so this is unlikely to be repeated.                                   |

The contraindications and precautions are not especially different in nature than other medicines available without prescription. In particular, NSAIDs such as diclofenac have been associated with increased cardiac risk.[50] Some non-prescription medicines increase blood pressure or heart rate, or are associated with gastric bleeding or narrow therapeutic index. Considerably greater screening will be conducted in supplying sildenafil than most existing non-prescription medicines, and consequently the risk is expected to be very low with sildenafil under the proposed reclassification.

A study of men in the UK self-assessing their suitability for sildenafil supply using the pack and pack insert found most men could do this on their own.[51] We have a higher safety margin than this, with involvement of especially trained pharmacists using a screening tool. The pack and pack insert provide a safety net for the consumer.

## **7. Possible resistance**

Not applicable

## 8. Adverse events – nature, frequency, etc.

Sildenafil is well tolerated,[5, 6] with a “substantial safety margin” and relatively short half-life of four to five hours.[5] The short half-life is advantageous in the OTC environment should adverse events occur. Adverse effects tend to be transient and mild to moderate. The most common effects are headache, flushing, dyspepsia and rhinitis. Adverse events are no more frequent in men taking antihypertensives than men not taking antihypertensives.[52]

In a meta-analysis of PDE5 inhibitors, serious adverse events were not statistically different versus placebo.[10] Giuliano, et al. collated safety data from 67 double-blind sildenafil trials for ED and manufacturer spontaneously reported postmarketing safety information.[5] In the trials, treatment-related serious adverse events occurred in 2 (0.1%) patients taking 50 mg or 100 mg sildenafil and 1 (0.1%) patients taking placebo. Serious adverse events are defined as having an outcome of death, being life-threatening, requiring inpatient hospitalization or prolongation of existing hospitalization or causing a persistent or significant disability or incapacity or a congenital anomaly. The post-marketing safety database included 3.3% of patients with an outcome of death.

Adverse effects are not significantly different between the 50 mg and 100 mg strengths, except for transient effects on colour vision which occur more commonly at doses  $\geq 100$  mg than at 50 mg, and men 75 years and over were more likely to get headache at a higher starting dose.[5]

Priapism is rare, with only 11 reports in the Pfizer clinical trials database (0.13% of sildenafil recipients vs. 0.03% of placebo), and 407 spontaneous post-marketing reports (a quarter of which reported concomitant medication that may have contributed).[5] This is warned about in counselling (see Appendix 3) and in the pack insert (Appendix 5), as it needs to be treated. Use with other ED medicine is warned against, and pharmacists will screen for conditions that predispose towards priapism, i.e. sickle cell anaemia, leukaemia and multiple myeloma (see Appendix 3).

The Pfizer clinical trials database received no reports of non-arteritic anterior ischaemic optic neuropathy (NAION).[5] NAION causes a sudden partial loss of vision in one eye which might be caused by ischaemia of arteries supplying the optic nerve.[53] Risk factors for NAION and ED are similar including increasing age, hypertension and diabetes, and up to 6000 cases of NAION are reported in the US each year. Medications postulated to contribute to NAION include sumatriptan, sildenafil, and nasal decongestants, but the relationship for none of these is certain.[54] Three hundred and thirty three spontaneous reports of NAION were received by Pfizer, nearly half of whom had predisposing risk factors (where medical history was known). NAION was no more common in US veterans prescribed PDE5 inhibitors for two years versus those who were not (relative risk 1.02).[10] Gorkin, et al. estimated 2.8 cases of NAION per 100,000 patient years exposure to sildenafil, which they considered did not suggest a causative role of sildenafil.[53]

Extensive study has shown no evidence of sildenafil increasing risk of adverse CV events.[5, 55] The overall CV death rate and incidence of serious CV events was comparable in the placebo group to the sildenafil group in the Pfizer clinical trials database.[5] Giuliano et al noted that “based on available safety data, there is no evidence of a causal link between sildenafil and cardiovascular events.”[5] Safety of sildenafil in men with diabetes mellitus, arterial hypertension or CV conditions is similar.

The Silvesta datasheet lists the adverse events from phase II/III studies as in Table 4.[6]

TABLE 4 ADVERSE EFFECTS FROM PHASE II/III STUDIES

| Adverse event           | Percentage of patients reporting event on sildenafil | Percentage of patients reporting event on placebo |
|-------------------------|--|---|
| Headache                | 16%  | 4%  |
| Flushing                | 10%  | 1%  |
| Dyspepsia               | 7%   | 2%  |
| Nasal congestion        | 4%   | 2%  |
| Urinary tract infection | 3%   | 2%  |
| Abnormal vision         | 3%   | 0%  |
| Diarrhoea               | 3%   | 1%  |
| Dizziness               | 2%   | 1%  |
| Rash                    | 2%   | 1%  |

The NZ Suspected Medicine Adverse Reactions (SMARS) database lists 27 reports with sildenafil as a suspected drug involved between 1 Jan 2000 and 31 Mar 2013, including one death. The summary is attached (Appendix 8). This level of adverse reactions compares favourably with a variety of medicines available in pharmacy and supermarkets (Table 5).

TABLE 5 SUSPECTED MEDICINE ADVERSE REACTIONS 1 JAN 2000 ONWARDS

| Medicine                                | Availability                                    | Reports   | Deaths   |
|---|---|-----------|----------|
| <b>Sildenafil</b>                       | <b>Proposed pharmacist-only</b>                 | <b>27</b> | <b>1</b> |
| Aspirin                                 | General sales                                   | 190       | 10       |
| Codeine                                 | Pharmacy-only/pharmacist-only                   | 93        | 0        |
| Dextromethorphan                        | General sales                                   | 29        | 0        |
| Ibuprofen                               | General sales/pharmacy only                     | 155       | 1        |
| Influenza vaccination                   | Exemption to prescription                       | 1952      | 0        |
| Iron and salts (excluding iron sucrose) | General sales/pharmacy only                     | 24        | 0        |
| Naproxen                                | Pharmacy-only                                   | 98        | 2        |
| Omeprazole                              | Pharmacy-only                                   | 816*      | 1        |
| Pseudoephedrine                         | Previously available in pharmacy-only medicines | 26        | 0        |
| Sumatriptan                             | Pharmacist-only                                 | 73        | 0        |

\*Excludes reports of ineffective drug

Note: All adverse events are included, both prescription use and non-prescription use

Source: Medsafe website <http://www.medsafe.govt.nz/Projects/B1/ADRSearch.asp> Search conducted 27 Jun 2013

Sildenafil may be cardioprotective. In small studies of patients with congestive heart failure (CHF) sildenafil improved the cardiac index, reduced systemic vascular resistance and aortic stiffness, and improved exercise time and quality of life.[52] Obviously pharmacists would not give sildenafil to someone with CHF.

## 9. Potential for abuse or misuse

Sildenafil is not addictive. It is not an aphrodisiac (does not stimulate libido) and there is no evidence of physical dependence or tolerance.[5] A very small number of reports (58) of psychological dependence (e.g. not wanting to initiate sexual activity without sildenafil) have occurred.[5]

There is no incentive to exceed the recommended dose. If more than 100 mg is taken, adverse events may be more likely (e.g. headache, flushing and priapism), cost per usage will rise, and effect is unlikely to be improved. The pharmacist will advise not to exceed the stated dose, and the information sheet will also do so. In real-life, exceeding the recommended dose is rare and not associated with new adverse events.[5] In fact, a NZ study found people tended to reduce their dose on their own accord to save money.[31] OTC supplies will be limited to eight tablets per consultation. The maximum dose will clearly be marked on packaging and in discussion with patients. Should the dose be exceeded in unusual instances there is a wide therapeutic index.

Sildenafil has long been accessed through illicit supplies (e.g. internet, night club, friends, drug dealers, "Dad's supply"),[56] yet reported adverse events have remained low. However, dangers of such supply exist including potential for use of counterfeit products and inability to screen people purchasing it in this way. OTC supply has been mooted,[2] including by independent academics[3, 4] as a means to help reduce the risks associated with such use. See Benefits, above, for further details.

Just over 1% of spontaneous reports to Pfizer involved intentional misuse, e.g. taking without ED and/or without a prescription.[5] ED mainly affects men over 40 years,[26] so we have used a minimum age of 35 years to reduce the risk of use without need. A case study from the UK (see Appendix 6) where a lower minimum age exists suggests that misuse is not a problem under the PGDs, given the inconvenience of screening and other means of availability. The even more extensive screening process in NZ is likely to be extremely off-putting for those without genuine need. In the rare case that might occur where a patient could lie about having ED and the pharmacist is not aware of this, the expense of use, the risk of headaches, and the requirement for screening and need to ask the pharmacist for it would probably make it a brief experiment. Pharmacists are well used to screening for misuse e.g. with long-term use of topical nasal decongestants, overuse of stimulant laxatives, or for use outside of indications, e.g. advance sales for oseltamivir, and given the mandatory training and accreditation we expect they will take their responsibilities very seriously with the screening and look for a genuine need. Furthermore, there will be a maximum that can be supplied of 8 tablets per consultation to minimize potential for misuse. As with the PGDs (Appendix 1), pharmacists will be able to refuse a sale without providing a reason should they have concerns about the supply.

Having small packs available from especially trained pharmacists provides a much safer supply route than illicit use. Users will be screened thoroughly, supplies would be recorded (and checked back on), and only product registered on the NZ market will be available. Advice from pharmacists and from the pack will be that screening is necessary, and not to share the medication.

It is possible that a woman might try this medication e.g. her partner's supply. The pack and pharmacist's advice is strong with respect to sharing. In the unlikely event that a woman may take the medicine, she will obtain no benefit and has reasonable likelihood of experiencing side effects including headache, flushing, and rhinitis.[57] Using the key words sildenafil or phosphodiesterase inhibitors, female and misuse provided only one hit on a Medline search, which was irrelevant. Should this be a problem in practice it would have arisen before now given the ready availability of this medicine on the internet. The pack insert advises this medicine is not for women.

As a pharmacy must do a thorough screening before supply and once a year, it is likely that a person will not shop around, but rather continue to get from the same pharmacy. This saves the time required for a further (unnecessary) full screening. As the pharmacy will keep records as required under the Pharmacy Council for provision of pharmacist-only medicines for chronic conditions



(Appendix 4), the pharmacist will be monitoring frequency of purchase. This will be kept as a paper record (Appendix 3), which may be later adapted as an electronic record. It will also be kept in the person's dispensing record, as per the Pharmacy Council requirement.

While we expect that pharmacy will take their responsibilities with sildenafil seriously, we suggest as part of the accreditation that pharmacists agree to be mystery shopped and are aware that their accreditation for supply is at risk should they fail to carry out the screening as required. This is similar to the PGD provision which allows for spot checks of pharmacists. Any such mystery shopping would have independent oversight.

## 10. Further information

Non-prescription availability of sildenafil is not new. Sildenafil has been available in pharmacies in the UK since 2007 through PGD.[1] We have been unable to find any published reports highlighting any problems, and one PGD has just been extended to an upper limit of 75 years of age (previously 65 years) suggesting confidence in the supply. The PGD case study (Appendix 6) provides confidence that such supply provides a useful service with little difficulty. In 2009, Aronson in the UK suggested expanding access to sildenafil through reclassification to a pharmacist supply category – similar to that in NZ – with monitoring by the pharmacist.[3] This is similar to our proposal, although we have gone further with mandatory training. The main reason that sildenafil has not been reclassified in the UK appears to be the requirement, given its centralized registration in Europe, that it must also go through the centralized reclassification process (i.e. for all of Europe and not individual member states).[2] European conservatism has many sources, but includes that one member state (Portugal) has no provision for pharmacist-only or pharmacy-only supply (i.e. all non-prescription medicines can be sold by non-pharmacy retailers).[25]

In developing our screening tool and training outline we have used input from community pharmacists, a general practitioner with a special interest in men's sexual health, a cardiologist, and a community pharmacist who has provided PDE-5Is under PGD in the UK. We have also sought feedback from pharmacy organisations, including the Pharmaceutical Society of NZ, the Pharmacy Guild and Pharmacybrands, and will include any further feedback from these organisations.

### *CV effects of sexual activity*

Sexual intercourse has a short effect on blood pressure and heart rate.[32] During foreplay both increase mildly. A greater increase occurs during the 10-15 seconds of orgasm, with a rapid return to baseline afterwards. *"Exposure to sexual activity is of short duration and constitutes a very small percentage of the total time at risk for myocardial ischemia or MI."*[32]

Sexual activity can trigger an MI in someone with a vulnerable atherosclerotic plaque. A meta-analysis showed that sexual activity precedes infarction onset in 1.1% of cases, far lower than heavy physical activity (6%), mild-to-moderate physical activity (29%), emotional stress (7%) and meteorological stress (4%).[58] Culic notes that MI *"onset occurs when hemodynamic stress caused by an external trigger disrupts a vulnerable atherosclerotic plaque, and haemostatic and vasoconstrictive forces may favor the formation of an occlusive thrombus."* Thus, using sildenafil at times of sexual intercourse may possibly be helpful given the vasodilatory effects. Giuliano et al analysed randomized placebo-controlled clinical trials data for over 14,000 men, and a postmarketing safety database of 39,277 patients, and could not find any causal link between cardiovascular risk and sildenafil use.[5] Furthermore, sexual activity as a trigger for MI is no more common now than in the pre-sildenafil era. A Swedish study from 1993-1994 found an MI was triggered by sexual intercourse in 1.3% of MI

sufferers.[59] People participating in more frequent sexual activity have smaller increases in risk than those with low activity levels.[32] In a person with a previous MI, sexual activity increases their chances of another MI briefly from 10 chances in 1 million per hour to 20 to 30 chances in 1 million per hour.[32]

Please see Appendix 9 for heart guidelines about sexual activity. In many cases of heart disease sexual activity is not discouraged.[32] The American Heart Association recommends that for those with coronary artery disease “*sexual activity is reasonable for patients with no or mild angina.*”[32] The 2012 American Heart Association guidelines note that “*PDE5 inhibitors are useful for the treatment of ED in patients with stable CVD*”, but of course note the contraindication with nitrates. We have taken a more conservative approach to management than recommended in these guidelines.

Sexual activity is an uncommon trigger of angina, triggering less than 5% of angina attacks, and typically in sedentary people with severe coronary artery disease for whom angina occurs with minimal physical activity.[32] Such people would not receive sildenafil through pharmacy supply. Our screening tool includes questions about angina (excluding anyone with angina), and the ability to have a five minute brisk walk (Appendix 3).

Sudden death is rare during sexual intercourse, with around 0.6%-1.7% of episodes of sudden death occurring during such activity, often after excessive food and alcohol.[32]

#### *CV risk assessment in pharmacy*

Given that ED can be a sign of coronary artery disease,[33] the screening tool includes a CV risk assessment (Appendix 3). This exceeds the UK PGD screening tool (for a comparison see Appendix 1). Training includes CV screening and how to measure BP (Appendix 2).

Cardiovascular risk assessment in pharmacy has occurred in many countries including Canada,[60] the US,[61, 62] Germany,[63] the UK,[64-66] Thailand,[67] and Australia,[68, 69] with studies often identifying people at high risk who have not been seen by a doctor. In NZ, pharmacy students are taught BP monitoring, taking a pulse, glucose monitoring and are expected to do CV risk assessment using NZ tables of CV risk. Some NZ pharmacies already do BP checks, usually for a small charge. A handful of pharmacies have measured cholesterol, but this has been limited by the expensive equipment, short-dated strips and free tests through doctors. Pharmacy brands pharmacies have recently encouraged BP checks in pharmacies for their Men’s Health week, and provide member pharmacies with comprehensive materials to aid CV risk assessment.

#### *ED as a sign of diabetes*

ED may be a sign of undiagnosed diabetes.[26] This will be covered in the training. The pharmacist will be considering this in the screening, asking the patient if he has excessive thirst or is passing urine often. The pharmacist will be looking at the person holistically, e.g. considering obesity and ethnicity.

#### *Pharmacy Capability*

Community pharmacists have proven themselves keen to meet the challenges of reclassifications. Most pharmacists undertook the training for the emergency contraceptive pill. Pharmacists took a responsible approach to oseltamivir.[7, 8] After the reclassification of trimethoprim, informal feedback with over 25 pharmacists around NZ showed that all were extremely positive about this reclassification.[70] By March 2013, 1482 had undertaken the training at their own or their employer’s cost. Pharmacists spoken to have seen this supply as a valuable addition to their service to the community and taken it very seriously. Furthermore, pharmacy organisations have funded

research into this world-leading reclassification, showing the importance the whole profession places on this area.

NZ community pharmacy has proven itself in other areas, lifting their scopes of practice in areas such as immunisations and proving themselves in the Pharmaceutical Society-led warfarin monitoring project.[9] Pharmacists receive four years of undergraduate training, followed by an internship that includes further training and examination. These health professionals are embracing the opportunity to work at the tops of their scopes of practice and make a greater difference in the lives of their community. Pharmacists will take the same responsible approach to supply of sildenafil, particularly given the mandatory training and requirements the pharmacist agrees to for their accreditation (see Appendix 2).

Pharmacists are used to conversations about sexual health and other sensitive matters. Sexual health may arise within a consultation about vaginal candidiasis, and will often occur within an emergency contraceptive supply. In the UK, chlamydia screening is available in pharmacy with azithromycin supplied in asymptomatic cases with a positive test.[71, 72] In the UK, the National Institute for Health and Clinical Excellence (NICE) has endorsed pharmacy provision of alcohol brief intervention for screening for and addressing alcohol misuse.[73] Research has shown pharmacies to be highly rated by service users as a place to obtain and discuss the emergency contraceptive pill.[74, 75]

#### *Previous research regarding ED screening by pharmacists*

Men with self-reported ED were recruited in the UK, Germany, the Czech republic and Spain to test a pharmacist-administered screening for suitability for sildenafil.[76] The tool was administered by community pharmacists to the men who then undertook a telephone consultation with a study physician. If the study physician and community pharmacist disagreed about suitability for sildenafil, a specialist in sexual medicine reassessed the case based on the questionnaire responses and pharmacist's and doctor's notes. Three hundred and forty six men completed the study. Most men (73%) felt very or quite comfortable answering such questions in their local pharmacy. The authors found *"...that community pharmacists are cautious and responsible in recommending sildenafil..."*. Most of the time the pharmacists and the doctors agreed (70% concordance). Where the pharmacist and the doctor did not agree, often the sexual medicine specialist agreed with the pharmacist's recommendation (90% concordance). However, in 13 cases, the pharmacist recommended supply inappropriately: cardiovascular symptoms with moderate exercise or cardiovascular problems (n=10), use with tamsulosin (n=1) and alprostadil (n=1) and painful erections (n=1). Of the 48 cases that the pharmacist found unsuitable but the doctor found suitable, the sexual medicine specialist confirmed 81% were unsuitable for pharmacist supply, usually on the basis of the study drug information sheet. The questionnaire used in this study is not readily available. However, this study has identified the need to make the tool straight-forward to use – this is why we have included within the tool instructions for referral if possible, and used pharmacist input on the tool. The study also suggests the need to ensure the training has worked, which is why we have questions following each module. Not passing the questions will require a repeat of the module.

#### *Low testosterone*

Low testosterone can cause ED.[26] Testosterone levels naturally decline about 1% per year from 40 years of age.[77] Some health professionals mainly in North America consider testosterone deficiency is being underdiagnosed (with a consequent increase in prescriptions), but others consider it a natural ageing process, and in Europe and NZ prescription numbers have remained static.[77] BPAC notes that ED is rarely caused by low testosterone levels, and *"routine testing of testosterone levels in males with erectile dysfunction in the absence of other symptoms of late-onset hypogonadism is not*

*recommended.*”[77] Some experts recommend screening for hypogonadism or hyperprolactinemia is restricted to those with clinical signs of hypogonadism or ineffectiveness of PDE-5 inhibitors.[10] The pharmacist (and the pack insert) will explain that ED is a common problem and should be discussed with their GP in order to consider potential causes. Reclassification of sildenafil has the potential to encourage an earlier conversation than otherwise with their pharmacist and then their GP, which provides an opportunity to screen for potential causative factors. Where testosterone is low, sildenafil would probably have little effect, and sexual desire is also low.[10] In treatment failure, patients would discontinue sildenafil and be encouraged to see the doctor.

#### *Lack of effect*

PDE5-inhibitors do not provide guaranteed success, but most men for whom sildenafil did not work initially responded after appropriate consultation including correct use of the drug, increasing to maximum dose, patient and partner expectations and multiple attempts.[5] This will be managed in pharmacy by use of comprehensive training including patient counselling, dose titration, relationship aspects and how to raise these discussions. A requirement of accreditation is that a private consultation room is available and offered, to enable this discussion. Additionally, a comprehensive pack insert and an accompanying website will further support pharmacy supply.

#### *Relationship issues*

Partners often support PDE5 inhibitor treatment, and express high satisfaction with the therapy.[30, 78] This includes NZ studies.[31, 48] Reasons for discontinuation of these medicines in NZ is more about cost of therapy and no further need for treatment (e.g. confidence resolved) than partner issues.[31] The partner should be kept informed. The training will include relationship factors, and an advice point for first time users is to suggest the man tells his partner. As relationship issues can cause ED or contribute to it, these are considered within the screening (Appendix 3).

#### *Justification for using full dosing for OTC*

The majority of men in clinical trials with an open phase used a dose of 100 mg in that phase.[5] The PGD case study from the UK shows 100 mg is typically used also (Appendix 6). Expert advice is that 100 mg is the most common dose, and some experts tend to start at 100 mg and down-titrate if necessary to gain confidence. As the datasheet recommends 50 mg as a starting dose and increasing to 100 mg, pharmacists will be required to follow this advice. Having the 100mg available will maximize the benefits to the patient. Furthermore, most adverse events have a similar incidence for 50 mg and 100 mg doses, so there is no need for a lower dose in the non-prescription environment.[5] To avoid the opportunity for dose confusion, and to include the supply within the prescription records for a patient, the pharmacist will label the medicine with the correct dose.

#### *Depression*

Depression can cause ED,[19] and ED can contribute to depression.[32] This will be addressed in the training as a potential cause and how to discuss this. Furthermore, the pack insert will note it as a potential cause and suggest a discussion with a doctor. Given under-recognition and under-treatment of depression, the American Pharmacists Association Foundation has suggested community pharmacists become more involved in the area of depression to aid clinical outcomes and quality of life.[79] A US study in which 3700 people were screened by pharmacists for depression showed a two-question (PHQ-2) and nine-question screening tool (PHQ-9) were useable in pharmacy by pharmacists with training in this area.[1] Referrals included five urgent referrals of people with suicidal ideation. Most people with a positive screening had taken appropriate action by follow-up. Pharmacists will refer to the doctor if depression is suspected. In most cases treatment may still be given at the pharmacist’s discretion, particularly since ED may be causing or contributing to their depression.

*Differences between the proposed NZ reclassification model and the PGD model in the UK*

The differences are outlined in Appendix 10. We have elected to treat men earlier than later – the PGDs require one year of symptoms prior to treatment. We believe there is potential benefit in providing earlier treatment, for example, reducing the potential loss of confidence and self-esteem. Even more important is the opportunity for early triaging where ED onset may suggest an underlying cause that needs identifying, e.g. diabetes, CV disease or depression. Thus, we consider having a more thorough screening and not delaying the presentation is a more patient-centered approach.

*Summary*

Sildenafil is a well-characterised medication with wide therapeutic index. Serious side effects are rare. We have undertaken a conservative approach to the reclassification of sildenafil. We have mandatory training, annual screening that goes beyond the PGD in the UK, and follow-up screening at each visit. The training is comprehensive to maximise the benefits of this reclassification and minimize potential risks. Pharmacists must pass the training in order to supply the medicine. Pharmacy has clearly shown a capability to step-up in their involvement in health, and will take a responsible approach to the supply of sildenafil. This reclassification provides benefit to persons with ED, enabling controlled access outside of doctor supply. This will encourage earlier conversations about this problem, allowing advice around lifestyle matters (e.g. stopping smoking, becoming active), and encouraging a full doctor check-up and discussion about ED with their doctor.