Sildenafil

- an oral drug for the treatment of male erectile dysfunction

Development and Evaluation Committee (DEC) Report
for the West Midlands Region
produced in collaboration with the
Midland Therapeutic Review & Advisory Committee (MTRAC)

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About West Midlands Development and Evaluation Service

The West Midlands Development and Evaluation Service produce rapid systematic reviews about the effectiveness of health care interventions and technologies, in response to requests from West Midlands Health Authorities. Each review takes 3-6 months and aims to give a timely and accurate analysis of the available evidence, generating an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

About InterDEC

West Midlands DEC is part of a wider collaboration with three units in other Regions (the Trent Working Group on Acute Purchasing, the Scottish Health Purchasing Information Centre and the Wessex Institute for Health Research and Development) who undertake similar evaluations on the effectiveness of health care interventions or services. This group, InterDEC, aim to share their work, avoid duplication and to improve the quality control of reports through setting standards and peer review.

Contributions of Authors

Amanda Burls wrote the main report, undertook the searches for data on effectiveness, liaised with researchers to obtain unpublished data, obtained the views of experts, reviewed the effectiveness data, independently assessing its quality and extracting data, and assisted with the economic evaluation and review of epidemiology and treatments. Wendy Clark reviewed the effectiveness data, independently assessing its quality and extracting data, and read and commented on the draft report. Lisa Gold provided the economic analysis and modelling of the possible impact of sildenafil, wrote Section 6 of the report and read and commented on the draft report. Sue Simpson did the research on the background epidemiology of erectile dysfunction (ED), undertook the telephone survey of current service provision for the treatment of ED in the West Midlands Region, and read and commented on the draft report.

West Midlands Development and Evaluation Committee Recommendation:

The recommendation for the use of sildenafil to treat male erectile dysfunction was:

Strongly Supported

Anticipated expiry date

- **This report was finished in September 1998**
- **The searches were completed in June 1998**
- **There are further trials known to be in progress. However, the evidence for effectiveness is strong and a large number of subjects would have to participate in trials producing conflicting results to reverse the conclusions.**
- **Data from some completed trials have not been published in full yet. This may give further information, particularly in relation to effectiveness in sub-groups.**
- **Insufficient time has elapsed to comment on the long-term safety of this drug or rare adverse events, and data on this should be reviewed as it becomes available.**

Contents

1 EXECUTIVE SUMMARY

1.1 The Problem

Definition

Male erectile dysfunction (ED) is the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection.[1]

Prevalence

It is a common condition affecting ~9% of the adult male population. It is estimated that currently less that 10% of men with ED seek medical treatment, although the proportion presenting has been increasing in recent years.

Causes

ED can be caused by psychological, neurological, hormonal, vascular or anatomical problems or a combination of such problems. Additionally, ED can be induced by drugs that interfere with the normal functioning of these systems.

Certain diseases predispose men to ED: up to 50% of men with diabetes and 40% of men with heart disease are thought to have some degree of ED. The prevalence of ED increases with age (around 1 in 3 men over 60 are thought to have ED) - this is thought to be due to the increase of the associated diseases with age rather than part of the natural ageing process.

Current service provision

Currently, ED is routinely treated in the NHS. Treatment is usually initiated in secondary care. There are specialist clinics in most Health Authority areas with waiting lists usually around 3 months. Standard treatments for ED, including intracavernosal injections, counselling, oral drugs, intraurethral alprostadil (MUSE) and surgery, are currently provided within the NHS. Many of these treatments have limited acceptability to users.

Technology evaluated

Sildenafil is a new oral treatment for ED and was licensed for use in male ED in Europe in September 1998[2]. It is marketed by Pfizer under the trade name Viagra®. This is the first oral drug to be marketed specifically for the treatment of male ED and was first launched in the U.S.A. in April 1998.

Quality of Evidence

A systematic review of all randomised controlled trials comparing sildenafil to placebo or any other therapy in men with ED was undertaken. Twenty-one trials were identified. Only 3 of these had been published in full at the time of review. Eighteen were available in the new drug application (NDA) submission to the FDA. Some of these have also been published in abstract form. Additional information about trial data was obtained from Pfizer. In clinical trials approximately 4,000 men have been studied of whom over 3,000 received sildenafil.

Direction of evidence

All trials showed a statistically significant improvement in erectile function in patients using sildenafil compared to placebo. About 75-80% of men show a clinically significant improvement in erectile or sexual function on sildenafil compared to ~25% on placebo. The number needed to treat to (NNT) was ~2. Many of the patients in the studies had some baseline erectile function and it is probable that in clinical practice, where the erectile function tends to be more impaired, the NNT may be higher.

The drug has a relatively safe side-effect profile. The major contraindication is concurrent use of nitrates.

Prescribing in primary care

There is wide agreement among urologists, pharmacists and GPs that the primary diagnosis of ED and its treatment with sildenafil can be undertaken safely and more efficiently in the primary care sector.

Cost-utility

There is a great deal of uncertainty surrounding the assumptions used to calculate the cost/QALY of treating erectile dysfunction with sildenafil. Our best estimate is approximately £7,000/QALY. Sensitivity analysis around the assumptions produces a range of cost/QALYs within the £3,000 - £20,000/QALY "strongly supported" decision band used by the Development and Evaluation Committee.

Implications for the NHS

If sildenafil were available for prescription in primary care we estimate that the drug costs to an avergae Health Authority with a total population of 500,000 would be between £750,000 and £1,250,000 per annum, depending on the percentage of men who present for treatment.

2 INTRODUCTION

The technology evaluated

Erectile dysfunction (ED) is the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection[1] and is thought to affect approximately 9% of male adults (see section 0, page 11).

Sildenafil (Viagra®) is a new oral drug specifically for the treatment of erectile dysfunction. It was licensed in U.S.A for the treatment of ED on the 27th March 1998 and marketed in mid-April. It was licensed for use across Europe in September 1998.

Objective of the report

This report looks at the effectiveness, safety and cost-effectiveness of sildenafil for the treatment of male erectile dysfunction compared to:

- placebo
- current treatments for ED

3 BACKGROUND

What is erectile dysfunction?

Definition

> ***Erectile dysfunction*** *is the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection.*

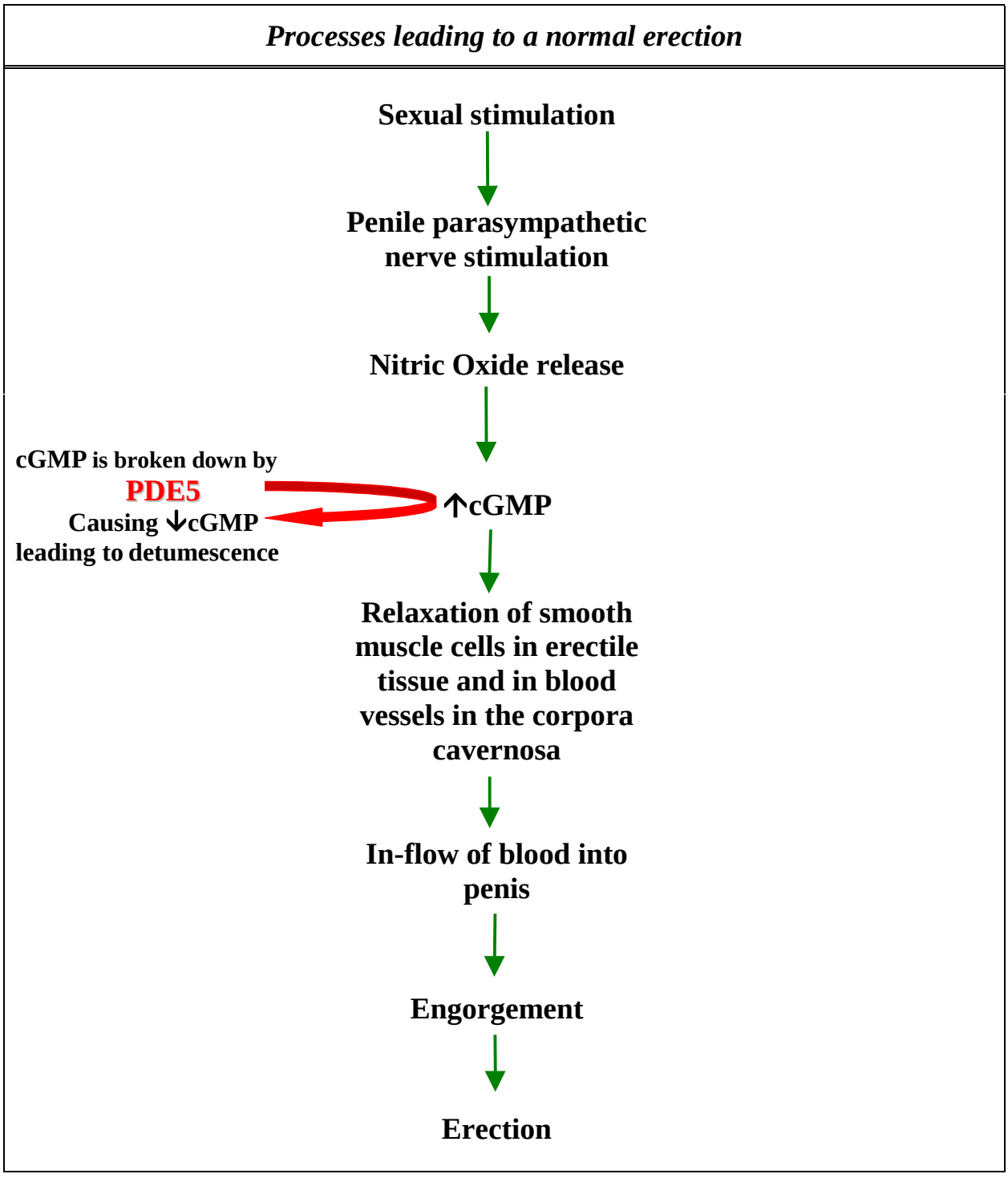
In 1992 the NIH Consensus Development Panel on Impotence in the U.S.A. defined male *erectile dysfunction* (ED) as "the inability to attain and/or maintain an erection sufficient to permit satisfactory sexual performance".[3] This definition has now gained widespread acceptance. It is similar to the American Psychiatric Association DSM (IV) definition of Male Erectile Disorder as "the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection".[1] The degree of ED varies and may range from a partial decrease in penile rigidity or ability to sustain an erection to complete erectile failure.[4; 5] The NIH panel concluded that the term *erectile dysfunction* should replace the more general term *impotence* which can carry pejorative connotations and is also used to refer to libidinal, orgasmic and ejaculatory problems.[6]

Classification of erectile dysfunction

> ***Erectile dysfunction*** *can be*
>
> - *Psychogenic*
> - *Organic*
> - *Mixed (organic and psychogenic)*
> - *Of no established organic cause*

The normal male erection is a complex event that results from the co-ordinated function of a number of psychological, neurological, hormonal and vascular systems (see Figure 1 - Normal erectile physiology, below). Disturbance of any of these can lead to ED.

Figure 1 - Normal erectile physiology



Erectile dysfunction is often broadly classified as *organic* or *psychogenic*:[6] *organic* refers to ED with a clear physical cause (e.g. spinal cord injury) or occurring in conjunction with a condition known to be a risk factor for ED (e.g. diabetes); *psychogenic* refers to all other forms of ED. In this dichotomous categorisation, which is widespread in the literature, "psychogenic" subsumes both ED where there is a clear psychogenic origin and all ED where no physical cause has been established.

As the knowledge of the pharmacology and physiology of erections has increased, new underlying organic causes of ED (which would previously have been categorised as *psychogenic*) have been identified. The strong interplay between psychogenic and organic factors[7] also limits the utility of this simple dichotomy: ED is often multifactorial in origin with psychological anxiety compounding organic problems.[8]

Some authors now reserve the term *psychogenic* to refer to ED of established psychological origin. *Organic* is still used to refer to ED with a physical cause or occurring in conjunction with a condition known to cause ED. Two further classifications are then made: *No established organic cause* for ED that does not fit into the above categories; *Mixed* where both organic and psychogenic factors are believed to play a role. This convention will be followed where possible in this report.

The clinical features of "pure" forms of psychogenic and organic disease are outlined in Table 1, below.

Table 1 - Features of organic and psychogenic erectile dysfunction

Psychogenic features	Organic Features
Sudden onset	Gradual onset
Specific situations	Occurs in all circumstances
Normal early morning and night-time erections	Loss of night-time and early morning erections
Relationship difficulties	Normal libido

Source: Dunsmuir W.D. & Holmes S.A.V.[9]

The effect on erectile dysfunction on the patient

Erectile dysfunction can lead to:

- *Low self-esteem*
- *Depression*
- *Anxiety*
- *Guilt*
- *Impaired perception of physical well-being*
- *Problems within relationships*
- *A detrimental effect on perceived quality of life*

Some men accept ED as part of the ageing process, for others it can be devastating,[10] leading to feelings of anger, guilt and low self-esteem.[11] The ability of people to have intercourse can be very important to their perception of well-being.[12] ED can have a profound impact on perceived quality of life.[5; 13; 14]

A survey conducted by the Impotence Association in 1997[15] on 432 patients found that 62% had reduced self-esteem.[a] Patients also said their quality of life was significantly affected, with 32% giving a rating of 8-10 (the scale goes from 1 = *no effect at all* to10 = *had an extremely detrimental effect*). It has been said that "the loss of potency is more than just the inability to have sexual intercourse".[16]

While only a small proportion of patients with complete ED seek medical help, many people spend a great deal of time and money seeking solutions elsewhere. The survey of people known to be concerned about their impotence by the Impotence Association[15] found that over a third of patients or their partners had purchased items such as devices, videos, books, creams etc. before seeking NHS medical help. Of these, nearly half (47%) spent over £100, with 8% spending over £1,000. Eighty six per cent of patients took actions before, or instead of, seeking help from their GP. Seventy seven percent of patients in the survey had eventually visited their GP about ED.[a]

[a] Caution must be used before generalising the results of the Impotence Association survey because the people who have contacted the Association are a self-selected group who are particularly concerned about the problem and are unlikely to be representative of all men suffering from ED.

ED often causes relationship problems and can affect a man's interactions with family and associates.[17] The Impotence Association survey[15] found that 21% of patients' relationships had broken up as a result of ED. Eight percent of partners had thought about breaking off their relationship because of their partners erectile problems. Seven percent of men with erectile dysfunction attending a behaviour therapy clinic for psychosexual counselling had such severe ED that their marriages had not been consummated.[18]

Although ED is widely accepted as having an adverse effect on quality of life, this is mainly based on anecdote and expert opinion: there is little good quality published data, obtained using validated instruments.

Prevalence

1. *Around 9% of the adult male population suffer from complete ED*
2. *The prevalence of ED increases steadily with age to around 1in 3 in men over 60*
3. *The prevalence of ED is higher in men with associated conditions, e.g.*
    - *Diabetes*
    - *Hypertension*
    - *Cardiovascular disease*

Erectile dysfunction is a common condition. It can be partial or complete. It is one of the most common serious sexual dysfunctions in men.[10; 19] It is difficult to be precise about exactly how many people suffer from, or are being treated for, ED for a number of reasons:

- Only a small fraction of men with ED present for treatment.
- ED presents in both primary and secondary care and is treated by a number of different specialties (e.g. urology, geriatrics, endocrinology, psychiatry, genitourinary medicine).
- Treatments are diverse and there is no easy way to quantify these with routine statistical data.
- Both patients and health care providers may be embarrassed and reluctant to discuss sexual function candidly and it is often under-diagnosed.[6]
- Cross-sectional studies to collect prevalence data are mainly of poor quality with unclear definitions of ED.
- ED can carry a stigma and is bounded by cultural, religious and legal issues:[20] people will often not respond, or respond inaccurately, to questions about ED. It is often under-reported.

Most papers that give information about prevalence cite other papers rather than providing new information. Most of these citations appear to be based on the data from Kinsey *et al*[21] from 50 years ago or Feldman *et al*[13] from the 1980's. Studies investigating the prevalence of ED, or impotence, in the general population are shown in **Table 2**, page 12, below.

From this data it can be seen that erectile dysfunction is strongly age related. The Massachusetts Male Ageing Study suggests that 52% of men aged 40-70 years have some degree of impairment in initiating or maintaining an erection (which is mild in 17%, moderate in 25% and complete in 10%).[13] This does not imply, however, that ED is part of the normal ageing process[3] - ED is caused by many conditions (and/or their treatments) which increase in prevalence with age.

Table 2 - Studies of prevalence of erectile dysfunction in the general population

Study	Year	Study size	Respondents	Prevalence of ED	Definition of term used *Comments*
Kinsey *et al*[21]	1938-1948	7,812	Males aged 20 to 80 years	<1% -30yrs <3% -45yrs 6.7% - 55yrs 25% - 65yrs 55% - 75yrs 75% - 80yrs	**Impotence – not further defined** *Interviews over a period of 10 yrs.*
Feldman *et al*[13]	1987-1989	1,290	Non-institutionalised men 40-70 years old in Boston, Massachusetts	52% - combined prevalence all ages (17.1% mild 25.2% moderate 9.6% complete) 67% - 70yrs Complete ED 5%- 40yrs 15%-70yrs	**Impotence – persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance** *A community based, random sample, observational study*
Malmsten *et al*[22]	1997	10,458	Men aged 45 years or older living in Goteborg, Sweden	7.6% - impotent 1.5% - at 45yrs 17.8% - at 80yrs	**Impotence – not further defined** *Postal questionnaire. Random sample of total population. Response rate 74%*
Jonler *et al*[16]	1995	1,517	Men attending a free screening programme for prostate cancer	7.7% has not had an erection in 12 months	**Impotence – presence of sexual erections** *Self-reported questionnaire.*
Ard[23]	1955	161	Couples married for 20 years. Mean age 47 years.	26% - once in a while 6% -sometimes 1% - usually 2% - almost always 1% - always	**Impotence – not further defined** *Self-reported questionnaire: "In the last 3 years, about how often have you experienced impotency during sexual intercourse with your wife?"*
Frank *et al*[24]	1978	100	'normal' sexually active couples. Predominantly white, Christian and well educated. Mean age of men 37.42 ±11.15 (SD)	7% - difficulty getting an erection 9% - difficulty maintaining an erection	**Sexual dysfunctions – difficulty getting/maintaining an erection** *Part of a larger study of "present-day" marriages. Couples asked to complete a 15 page self-report questionnaire.*
Gebhard & Johnson[25]	1938-1963	5,637	Males aged 15+	5.6 – 19%	*"Have you ever had trouble getting or keeping an erection?"*
Diokno *et al*[26]	1989	283	Men aged 60 yrs and over in Washtenaw County, Michigan.	40% - had difficulty getting or maintaining an erection 13% has no erection at all	**Erectile impotence - difficulty getting or maintaining an erection** *Questions about sexual activity included in a clinical examination*
Slag *et al*[27]	1983	1180	Males at a medical outpatient clinic at the Minneapolis Veterans Admin. Medical Centre. Mean age 59.4 +/-0.7(SEM)	34% - impotent	**Impotence/erectile dysfunction – not further defined** *Interview*
Schein *et al*[28]	1984-1985	64	Family practice patients Aged 18-78 (mean=35yrs)	27%	**Problems with arousal** *Self report questionnaire*
Nettelbladt & Uddenberg[29]	1978	58	Married Swedish men	7%	**Impotence – not further defined** *Semi-structured interviews.*
Cogen & Steinman[11]	1990	87	Elderly men attending a geriatric outpatient clinic at the Philadelphia Veterans Admin. Mean age 72.6 yrs (Range 61-84).	28% - complete loss of erectile function 31% - frequent difficulties achieving an erection suitable for intercourse	**Erectile dysfunction – inability to achieve or maintain an erection suitable for penetration** *Questionnaire administered by the patient's clinic physician*
Spector & Carey[30]	1990	N/A	N/A	4-9% - male erectile disorder	*A review of 23 studies on the incidence and prevalence of sexual dysfunction*

Aetiology of erectile dysfunction

Causes of erectile dysfunction *include problems that are*

- *Psychological*
- *Anatomical*
- *Neurological*
- *Hormonal*
- *Vascular*
- *Drug related*

A higher prevalence of ED is found in patients with chronic illnesses including diabetes mellitus, heart disease, hypertension and several neurological disorders (see list, below). This association is thought to be due in part to the disease processes and in part to their treatments (e.g. drugs, surgery, radiotherapy).

Figure 2 - Diseases associated with erectile dysfunction

Type of Disease	***Disease***
Systemic	Atherosclerosis Diabetes mellitus Arterial hypertension Myocardial infarction Scleroderma Renal failure Liver cirrhosis Idiopathic haemochromatosis
Neurogenic	Epilepsy Cerebrovascular accidents Multiple sclerosis Guillain-Barré Alzheimer's disease
Respiratory	Chronic obstructive pulmonary disease
Endocrine	Hyperthyroidism Hypothyroidism Hypogonadism
Penile	Peyronies disease Epispadias Priapism
Psychiatric	Depression Widower's syndrome Performance anxiety
Nutritional	Protein malnutrition Zinc deficiency
Haematological	Sickle cell anaemia Leukaemias
Infectious	Brucellosis Tuberculosis AIDS Trypanosomiasis

Source: adapted from Benet A.E & Melman A.[20]

Studies that look at the frequency of ED in different disease groups are summarised in Table 3 - Prevalence data for different disease groups, below.

Table 3 - Prevalence data for different disease groups

Population	No. of males in population (E&W)	Prevalence of ED	
		Complete ED	Undefined ED
General male population[21 23]			
30 year olds	439,000[a]		<1%[21]
40 year olds	345,100 [a]	5%	
65 year olds	235,500 [a]		25%[21]
70 year olds	207,200 [a]	15%	
80 year olds	98,100 [a]		75%[21]
40-70 year olds	8,889,300 [a]	9.6%	52%[13]
61-84 year olds	4,074,600 [a]	28%	
Diabetes -diagnosed[d]			
All ages	86-132/10,000[c]		23-35%[13; 27; 31; 32]
IDDM (Type I) *All ages*	26-46/10,000 [c]		20%[33]
NIDDM (Type II) *All ages*	68-100/10,000 [c]		71%[34]
55-64 year olds	100-200/10,000 [c]		56%[34]
65-74 year olds	200-334/10,000 [c]		65%[34]
Hypertension			
Treated	~870 per 10,000 [b]		8-49%[13; 32; 35]
Untreated	~1,600/10,000 [b]		8-49%[13; 26; 32; 35]
Coronary Heart disease			
Treated - all ages	~220/10,000 [c]		39-64%[13; 26; 32; 36]
Untreated - all ages	~690/10,000 [c]		39-64%[13; 26; 32; 36]
Multiple sclerosis	14 per 10,000 [e]		62-75%[37; 38]
Prostatectomy - all ages TURP Radical Prostatectomy	 18/10,000[f] 0.6/10,000 [f]		 0-40%[39-41] 9-75%[42; 43]

a ONS – based on 1991 census data

b 1996 Health Survey for England

c Health Care Needs Assessment, First Series, 1994

d The ratio of diagnosed to undiagnosed diabetes is thought to be around 1:1. The above figures for the prevalence of ED due to diabetes mellitus are likely to be higher

e MS Society data

f 1996/7 Hospital Episode Statistics

Cardiovascular disease

Hypertension is often cited as a risk factor for erectile dysfunction. In people with untreated hypertension, 8-10% are said to have ED at the time they present.[35] In a study of impotent men aged 40-79 years (mean 60.9) 48.6% had hypertension and 38.9% had atherosclerosis.[32] It is difficult to determine how much of the increased prevalence of ED in men with hypertension is due to the disease and how much to the treatment.

A number of studies have reported the prevalence of erectile dysfunction in patients following myocardial infarction. These ranged from 50% [35] to 64% [26; 36]

The Massachusetts Male Ageing Study[13] found that the age-adjusted probability of complete impotence was 39% in those with treated heart disease and 15% in those with treated hypertension, compared with 9.6% in the entire sample.

Endocrine disorders

Diabetes

Diabetes causes vascular and neurological damage and is therefore one of the systemic disorders most frequently associated with ED. ED is more common in the diabetic than the general population and occurs at a younger age.[9] In men in their early thirties it is three times more common than in the general.[44] This relative risk reduces to two-fold greater in men with diabetes than in men in the general population by the age of sixty. However, the prevalence of ED is greater in diabetic patients treated with insulin or oral hypoglycaemic agents than those who control their diabetes by diet alone.[31] Estimates of prevalence of erectile dysfunction have ranged from 7-85%[45] in samples of diabetic men. A number of studies of prevalence are summarised in, Table 18 - Studies of prevalence of erectile dysfunction in male patients with diabetes, page 50.

Other endocrine disorders

Other endocrine disorders are also important organic causes of impotence. Some reports suggest that between 6%-45% of cases may have an endocrine origin, with hypogonadism being the most common endocrine cause.[8] A study of impotent men aged 40 to 79 indicated a high prevalence of endocrine disorders - hypogonadism was diagnosed in 23% of the patient population.[32]

Multiple Sclerosis (MS)

Sexual dysfunction is very common in patients suffering from Multiple Sclerosis (MS). A questionnaire sent to MS patients (mainly with severe symptoms) asking about their sexual life[37] found that 91% of male patients' sexual life had changed. Disturbances in erection (i.e. loss of erection, weak erection, periodical loss of erection) were the most common problem (62%). Erection was normal in only 20% of males. In a further questionnaire study carried out on 68 male patients with MS, sexual dysfunction was reported by 75% of respondents, 63% said they had difficulty in achieving an erection and 52% had difficulty maintaining an erection.[38]

Surgery

Impotence is common after radical pelvic surgery, for example resection for bowel cancer.[42] The incidence of ED following pelvic fracture with associated urethral distraction injury is reported to be 2.5%-62%[46] and the aetiology is normally neurogenic.

Erectile impotence has been reported in 0-40% of men who have undergone transurethral prostatectomy.[39-41; 47; 47] The risk of impotence is thought to be fairly low in men who are fully potent before surgery. It is higher in men who already have a degree of erectile failure and is thought to be related to the incidence of capsular perforation at the time of surgery and therefore damage to the neurovascular bundles.[41] The overall risk also appears to increase with age and prostatic size.[39]

Impotence after a radical prostatectomy results from damage during the surgical procedure to either nerves or blood vessels that supply the penis. Three research studies in recent years on incidence rates of ED after nerve-sparing radical prostatectomy for the treatment of prostate cancer, reported overall incidences of 28%, 32% and 42%.[42] The prevalence of ED after radical prostatectomy is increased with the age of the patient. A study of 503 men who had had a radical prostatectomy revealed an impotence rate of 9% in men younger than 50 years old, 25% in men 50-60, 42% in men 60-70, and 75% in men older than 70 years.[43] There is also an increased rate of impotence with increasing stage of tumour and excision of neurovascular bundles. The average overall rate of impotence after a radical prostatectomy is 34%.[42]

Drug related

Around 25% of ED seen in clinic patients is caused by medication, in particular thiazide diuretics and, to a lesser extent, β-blocking drugs.[8; 27] The Massachusetts Male Ageing Study[13] found that complete impotence was significantly more prevalent in men taking certain medications (hypoglycaemic agents (26%); anti-hypertensives (14%); vasodilators (36%); cardiac drugs (28%)) than in the sample as a whole (9.6%). Up to 75% of patients in alcohol rehabilitation programs are also thought to have ED. (See

Appendix 2 - Drugs associated with erectile dysfunction, page 55, for a list.)

Geographic, racial, ethnic, cultural and social variations

Very little is known about variations in prevalence of ED across geographic, racial, ethnic, socio-economic and cultural groups.[6]

Current treatments for erectile dysfunction

The choice of treatment/therapy will depend on the likely aetiology of the ED. Figure 3 - Erectile function and mechanism of action of treatments, page 17, gives the mechanism of action for different treatments for ED. The NIH consensus development statement proposed that, as a rule, the least invasive or dangerous procedures should be tried first.[3] The ideal goal in the treatment of ED is the restoration of erectile capacity with a minimally invasive and safe treatment.[48] Treating sexual dysfunction is aimed to improve quality of life.[12]

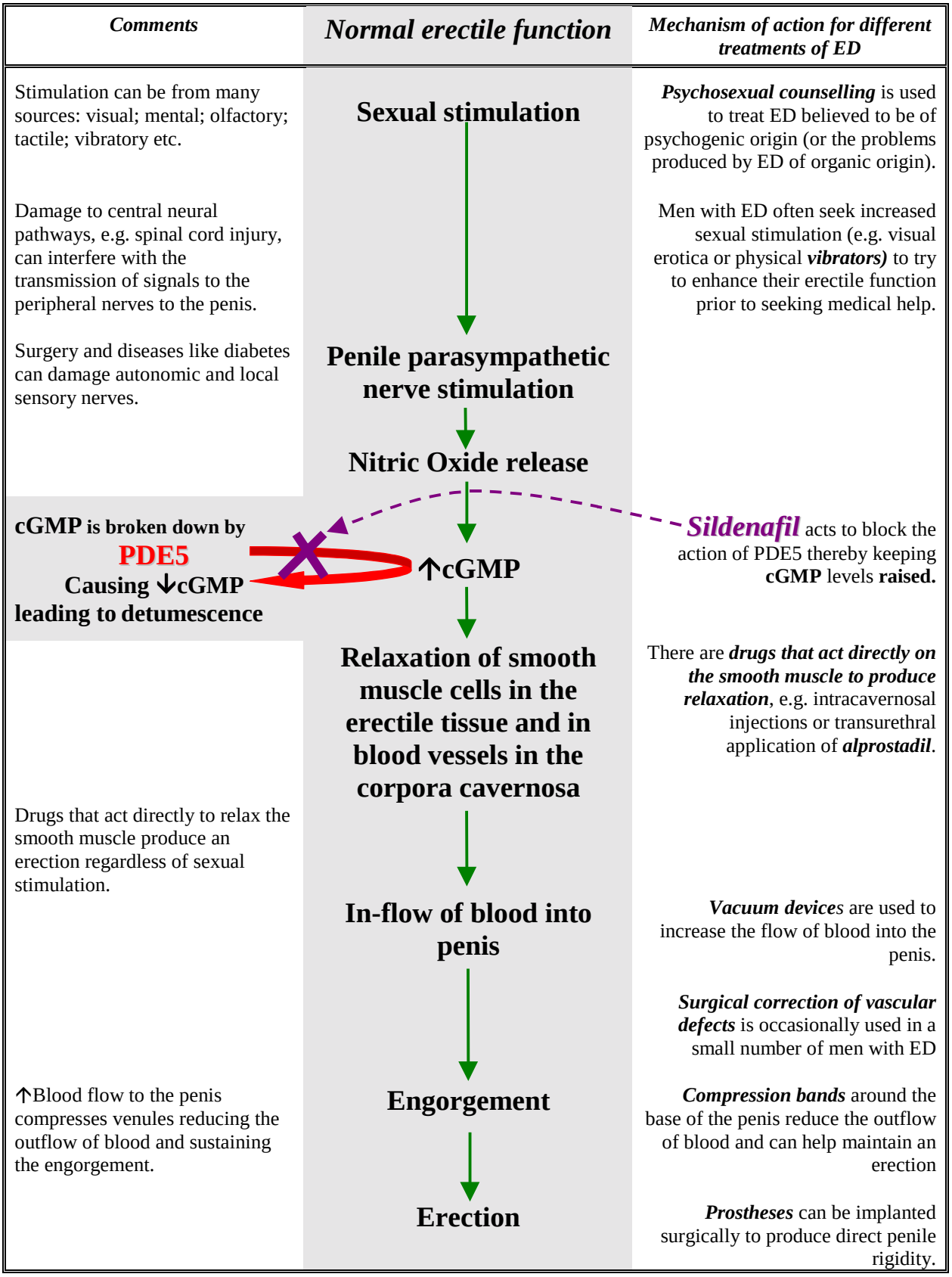
The American Urological Association (AUA) guidelines on the treatment of ED produced in January 1997,[49] recommended the use of three therapies; vacuum constriction devices, vasoactive drug injection therapy (with alprostadil as first choice) and penile prosthetic implants. Last year a transurethral formulation of alprostadil (MUSE) was launched in the UK. This has increasingly been used as the treatment of first choice in new patients presenting with erectile dysfunction without a specific treatable aetiology. The American guidelines are yet to be updated to include the new transurethral and oral treatments for ED.

Vacuum constriction devices

An erection is achieved by creating a vacuum around the penis, which draws blood to the corporal tissue, causing tumescence. Once the penis is erect, a constriction band is placed around the base of the penis to maintain the erection by reducing venous outflow. The tube is then removed and the patient can have sexual intercourse.

Vacuum devices can provide a safe, non-surgical and reversible method of obtaining adequate erections in up to 90% of patients.[19; 50] This is the cheapest form of treatment in the longer term. Devices are not available on NHS prescription although some NHS clinics provide them free of charge. The patient must be motivated to learn how to use the device efficiently and it should be acceptable to both patient and partner. Vacuum devices have been found to be more acceptable for older men in longstanding relationships than for younger men. The devices may be difficult for some patients to use, especially for those with impaired manual dexterity. Some men are reluctant to use them as they interfere with spontaneity.[51] The penis can feel cold because of the restricted blood flow and this can be unacceptable to some men or their partners.[9] The Impotence Association survey[15] found that only 30% of patients trying this therapy were satisfied and continued to use it. Complications are minimal but include bruising,[52] and impaired or absent ejaculation which can cause discomfort.[3]

Figure 3 - Erectile function and mechanism of action of treatments



Intracavernosal drug delivery

In 1982 it was shown that an erection can be produced by injection of a smooth-muscle relaxant into the corpus cavernosum.[53] Intracavernosal injection therapy involves the injection of a vasoactive drug or a combination of drugs directly into the penis. The drugs simulate the natural erectile process by relaxing the smooth muscle of the erectile tissue and dilating blood vessels, thus allowing erection to occur.

Most patients suffering from ED can have some success with intracavernosal injection therapy. Clinical experience has shown that this treatment can be effective in ED associated with vascular, neurological, psychogenic and hormonal difficulties.[54] Papaverine, phentolamine, phenoxybenzamine, alprostadil (prostaglandin E1) and moxisylyte are all available for intracavernosal injection. Alprostadil is the most widely used. Side effects include: pain, with or without burning (20%); priapism (1%); penile fibrosis (3%); penile deviation (4%).[55; 56] A bruise is common with any injection into the penis and it can sometimes cause alarm.[57] Priapism (inappropriately persistent erections) is the most serious side-effect. If an erection lasts for longer than 6 hours there is a danger that intracavernosal hypoxia may occur. This can result in fibrosis of the trabecular smooth muscle possibly preventing further erections.[51] Priapism is treated with adrenergic agents.[3]

Three separate multi-institutional, prospective studies in men with erectile dysfunction concluded that intracavernosal injection of alprostadil is an effective therapy with tolerable side effects. (NNT ~2) (see **Table 19**, page 51.)). Self-injection of prostaglandin E1 has also been shown to improve quality of erections, frequency of sexual activity, sexual satisfaction and improvement in psychological wellbeing (mental health, social health and self-esteem) in men with erectile dysfunction.[12; 58]

Combinations of these drugs are often used. Only alprostadil and moxisylyte are specifically licensed for the treatment of ED in the U.K.

Whilst intracavernosal injection has proven effectiveness, there is a high rate of patient dropout, often early in the treatment. Some studies report drop out rates of 21%,[54] while others report drop out rates as high as 80%.[59] Less than 50% of men commencing intracavernosal therapy continue treatment over the longer term.[60] The Impotence Association survey[15] found that only 31% of patients using this treatment were satisfied and continued to use it. Unsurprisingly, in a study of 200 patients in the UK, nobody chose the injection of the penis with drugs as the method of choice in response to the question “How would you best like to use a medicine to improve erections?".[61]

Transurethral drug delivery

A recent innovation is the insertion of a pellet of alprostadil directly into the urethra.[62] The alprostadil is absorbed through the urethral epithelium to induce an erection. A drug delivery system known as MUSE (Medicated Urethral System for Erection) has been developed to assist application. Clinical trials indicate that approximately 50-60% of men achieve satisfactory response during the course of treatment (NNT is ~4[b] (see **Table 19**, page 51).[7; 62; 63] Adverse reactions are similar to those seen with intracavernosal injections.[62-64]

Penile prostheses

Penile prostheses are surgically implanted devices that improve rigidity.[10] Implantation is invasive, expensive and irreversible.[62] It is usually only recommended to patients when other treatments fail. Three forms of penile prostheses are available: semi-rigid, malleable and inflatable. The effectiveness, complications and acceptability vary among the three types, with the main problems being mechanical failure, infection, and erosion.[3] Aseptic methods and conditions during surgery are required during insertion, which is normally carried out under a general anaesthetic.[52] There is also a risk of the need for re-operation with all devices, with the inflatable prostheses having the highest rate of failure requiring re-operation.[3]

Vascular surgery

[b] Other reviews of sildenafil,[166; 167] quote a number needed to treat (NNT) of ~2 for MUSE because they cite data for a highly selected group on whom the drug was tried (men who were known responders to intraurethral alprostadil) .[62] The figure of ~4 adjusts for all patients with ED presenting in the trial.

Reports suggest that direct surgical intervention to improve vascular inflow or inhibit venous return should be reserved for a very select group of patients.[3] The success rate of vascular surgery ranges from 31-80%.[62] The best candidates are younger men with discrete lesions in the pudendal artery, the common penile artery, or both, (due to pelvic or perineal trauma) rather than older men with more generalised atherosclerotic occlusive disease involving the cavernosal artery.[5]

Oral drugs

Oral drugs are a new development and are likely to prove to be more acceptable than current direct injection treatments.[65] Oral drugs that are currently available or in development are outlined in Table 4 - Oral drugs, their site of action and probable mechanism of action, below. Only sildenafil is currently licensed for use in treating ED in the UK.

Sildenafil citrate (Viagra®) was licensed by the Food and Drug Administration in America on 27th March 1998[66] and was licensed for use in Europe in September 1998.[2] Unlike previously approved treatments for ED, sildenafil does not directly initiate an erection, but potentiates the response to sexual stimulation.

Table 4 - Oral drugs, their site of action and probable mechanism of action

Drug	*Site of Action*	*Probable Mechanism of Action*
Sildenafil (Viagra®)	Peripherally acting agent	Phosphodiesterase inhibitor
L-Arginine	Peripherally acting agent	Nitric oxide precursor
Yohimbine	Centrally acting drug	Adrenergic receptor blocking agent
Delquamine	Centrally acting drug	Adrenergic receptor blocking agent
Phentolamine	Centrally acting drug	Adrenergic receptor blocking agent
Apomorphine	Centrally acting drug	Dopamine receptor agonist
Bromocriptine	Centrally acting drug	Dopamine receptor agonist
Trazodone	Centrally acting drug	Serotonin receptor blocking agent

(Source: adapted from Eardley[65])

Yohimbine

Yohimbine has been the subject of formal clinical trials since 1982. It is thought to act centrally and is indicated for the treatment of psychogenic ED. A clinical guidelines panel on ED in America in 1996 reported that outcome data for yohimbine indicates a therapy with marginal efficacy and does not see a significant role for it in the treatment of organic ED.[67] The drug is thought to be well tolerated, although hyper-anxiety, agitation and sweating may occur.[35] Hypertension has also been reported and is a contraindication of the use of the drug. It is available on a named patient basis in the UK for the treatment of psychogenic ED.

Phentolamine (Vasomax®)

Phentolamine (Vasomax®) has been used for penile injection for a number of years. In 1988, it was shown to be effective orally and has since been shown to cause an erectile response in 42% of men with psychogenic or mild vascular impotence.[7]

4 CURRENT SERVICE PROVISION

Erectile dysfunction is widely accepted as a health care need and routinely treated on the NHS. Treatment is usually initiated in secondary care. There are specialist clinics in most Health Authority areas with waiting lists usually around 3 months. Only a small proportion of men with erectile dysfunction present for treatment.

All standard treatments for ED are provided including intracavernosal injections, counselling, oral drugs, MUSE and surgery.

Erectile dysfunction is currently treated in most Health Authorities (HAs) within the NHS. Some HAs are said not to fund treatment currently for ED (Personal communication, Department of Health, July 1998) but none were identified in the West Midlands region - a telephone enquiry of all HAs in the West Midlands Region did not reveal any that refuse to pay for treatment for ED (although one was unable to provide information). The perception that treatment for ED is available routinely throughout the West Midlands is confirmed by a telephone survey of urologists and erectile dysfunction clinics across the region (see Table 17 - Telephone survey of erectile dysfunction and impotence clinics in the W. Midlands, page 49). Similar findings were obtained in the Anglia and Oxford Region in a telephone survey in August 1998 (Personal communication, Richard Wilcox, ACET, 10 August 1998).

Most patients currently being treated for ED have their treatment initiated in secondary care by consultants from various specialties including urologists, genitourinary physicians, diabetologists, endocrine specialists, psychiatrists, geriatricians and general physicians.[68]

The telephone survey of urologists and impotence specialists in the West Midlands revealed that all ran an 'impotence' clinic or were linked with nurse-led 'impotence' clinics (see Table 17, page 49). There was at least one erectile dysfunction clinic in every Health Authority area of the West Midlands Region. The frequency of these clinics was usually weekly (ranging from three times per week to monthly). There were around 10 new patients at most clinics. Waiting lists varied from none to 1 year (median 3 months). The most common treatments recommended were MUSE, Caverject (Alprostadil) and Vacuum devices. The demand for impotence treatment had grown (about two-fold) since MUSE became available last year. Since the marketing of sildenafil in the U.S.A., in March and April this year, there has been an even greater increase in enquiries.

It is estimated that less than 10% of men with ED currently seek medical treatment,[11] and less than 5% of men with ED receive treatment,[10] although 95% of cases are thought to be treatable. The belief that most impotence is psychological is considered a key factor which deters men from seeking treatment. Moreover the threshold at which men will seek treatment for ED has been high until now because of social stigma[15] and a perceived lack of convenient, safe and effective treatments.[63] Current prescribing in the West Midlands confirms this national picture. In 1997, based on PACT data, 61,926 injections of alprostadil were prescribed in the West Midlands region at a cost of £562,349 (see Table 5, below).

Table 5 - Annual cost of intracavernosal alprostadil in the West Midlands

Current Prescribing		
Strength of Injection	**No. of Injections Prescribed**	**Regional annual cost**
5	1,179	£7,967
10	22,630	£175,180
20	38,117	£379,202
Total	**61,926**	**£562,349**

Assuming 1 injection is administered per week, only 1,190 patients received alprostadil treatment in 1997, 0.06% of total regional male population aged over 16 (i.e. ~0.6% of the total ED population).

5 PROPOSED SERVICE PROVISION

The proposed new technology - sildenafil

Sildenafil citrate is a novel drug for the oral treatment of erectile dysfunction. It is a selective inhibitor of type 5 phosphodiesterase (PDE5) . This enzyme breaks down cyclic guanosine monophosphate (cGMP) which is a second messenger that amplifies the parasympathetic neural stimulation to produce smooth muscle relaxation in the corpora cavernosa and engorgement of the penis (see **Figure 3 - Erectile function and mechanism of action of treatments**, page 17).

Theoretically the drug could be used in primary or secondary care. Pfizer are marketing this drug as suitable for prescribing by primary care physicians and have begun a large educational programme about erectile dysfunction directed at primary care (*Erectile Dysfunction in Primary Care* EDiPC).

6 METHODS

Types of study sought

All randomised controlled trials (RCTs) comparing sildenafil with placebo or alternative therapies.

Search Strategy

Electronic Databases

The following electronic databases were searched for all articles containing the free-text terms "sildenafil" or "Viagra". There were no language restrictions.

- Medline 1966 - June 1998
- EMBASE 1988-June 1998
- Cochrane Library 1998 Issue 3
- PsychLIT 1996 -1987
- National Research Register Interim version - June 1998
- Pharmline

Internet

The main search engines were used using the terms "sildenafil" or "Viagra"

Hand searching

The FDA Centre for Drug Evaluation and Research, Joint Clinical Review for NDA-20-895 Viagra (Sildenafil), the BMJ, Lancet, JAMA, NEJM BJGP, Drug, Inpharma and Scrip were hand searched.

Personal contacts

The pharmaceutical company, Pfizer Ltd, was contacted, as were experts in the field. Where trials were only available in abstract form, further information was requested from Pfizer, in particular about the unpublished trials.

Follow up of references

References of all relevant studies identified were searched for further trial citations.
The Science Citation Index was searched using all relevant studies identified by the above procedures.

Quality assessment

An assessment of quality was undertaken independently by two researchers (AB, SS).

Data extraction

Two researchers (AB, WC) extracted the data from all trials independently into pre-defined tables. Discrepancies were resolved by discussion. (All discrepancies were due either to conflicting reporting of results in multiply-reported studies or simple transcription errors.)

7 RESULTS

Twenty-one RCTs were found, involving approximately 4,000 patients. All trials showed a statistically significant effect of sildenafil compared to placebo regardless of the underlying aetiology of ED.

About 75-80% of men show a clinically significant improvement in erectile or sexual function on sildenafil compared to ~25% on placebo. The number needed to treat to (NNT) is ~2.

Number of studies identified

Trials found

A total of 20 trials meeting the predefined criteria of "randomised controlled trials comparing sildenafil with placebo or alternative therapies" were identified in the literature. All compared sildenafil to placebo. All appear in abstract form in the Center for Drug Evaluation and Research Joint Clinical Review on Viagra[tm] (Sildenafil) NDA-20-895. Of these, only three studies (study numbers 102,[69] 103[69] and 351[70]) were published in full at the date of searching (to 30/06/98). Others are in the process of being submitted for publication (Pfizer, personal communication, 9th June 1998). Pfizer provided us with further information in the form of the protocols and unpublished study reports relating to key phase III trials (studies 102,[71] 103,[72] 104,[73] 106, [74] 361,[75] 363,[76] 364[77], 367[78]).

In their literature Pfizer refer to 21 RCTs (e.g. page 5 of Draft Package Insert for USA[79]). We contacted Pfizer about the discrepancy. The missing trial cited is study 166-301. This study has not been published and was not included in the FDA-NDA 20-895. A study report synopsis has been supplied by Pfizer.[80]

Missing trials

There are 13 studies mentioned as "not reviewed" in the Joint Clinical Review for NDA-20-895: Description of clinical data sources (in *Table 7 - Studies not reviewed in detail*).[81] Eleven are phase I studies and therefore do

not meet the inclusion criteria for this review. The other two are phase II studies: one is study 166-301, mentioned above; the other is study JP-96-602 which looked at the use of sildenafil capsules in Japanese males. Pfizer inform us that there are in fact two Phase II Japanese studies: one involved 60 patients and the other involved 250 patients (Pfizer, personal communication, 11th August 1998). No details are available on these trials although the outcomes for the subjects in these trials is included by Pfizer in their safety database.[81]

We contacted Pfizer about gaps in the study numbering (e.g. 252) to see if these represented missing or incomplete trials and were told that these were trials that did not take place (Pfizer, personal communication, 11th August 1998).

Table 6 - All Phase II and Phase III trials identified

All are randomised, double-blind and placebo controlled			
Type of trial is coded by shading:	= Phase II trials with evaluation of penile rigidity following visual or vibratory sexual stimulation as outcome measure	= Phase II with clinical outcomes	= Phase III trials

Study Number	**Source of information (P) = published in full (Abs) = abstract**	**Cause of ED in population tested**	**No. of patients**
101	FDA-NDA-20-895[82] (Abs) Leu *et al* 1997[83] (Abs)	Broad aetiology (excl. spinal cord injury)	416
102	FDA-NDA-20-895[84] (Abs) Goldstein *et al* 1998[69] (P) Pfizer Study Report[71]	Broad aetiology (excl. spinal cord injury)	532
103	FDA-NDA-20-895[85] (Abs) Goldstein *et al* 1998[69] (P) Pfizer Study Report[72]	Broad aetiology (excl. spinal cord injury)	329
104	FDA-NDA-20-895[86] (Abs) Rendell *et al* 1998[87] (Abs) Pfizer Study Report[73]	Diabetes	268
105	FDA-NDA-20-895[88] (Abs)	Broad aetiology (excl. spinal cord injury)	54
106	FDA-NDA-20-895[89] (Abs) Pfizer Study Report[74]	Broad aetiology (excl. spinal cord injury)	497
350	FDA-NDA-20-895[90] (Abs)	No established organic cause	16
351 (Part I)	FDA-NDA-20-895[91] (Abs) Boolell et al 1996[70] (P)	No established organic cause	12
(Part II)	FDA-NDA-20-895[91] (Abs) Boolell *et al* 1996 (P)[70]	No established organic cause	12
353	FDA-NDA-20-895[92] (Abs) Dinsmore WW *et al* 1996[93] (Abs)	No established organic cause	351
355	FDA-NDA-20-895[94] (Abs) Eardley I *et al* 1996[95] (Abs)	No established organic cause	44
356	FDA-NDA-20-895[96] (Abs) Bailey et al 1997[97](Abs) Virag R et al 1996[98](Abs)	Broad aetiology	205
357	Boolell *et al* 1996[99] (Abs) FDA-NDA-20-895[100] (Abs) Boolell et al 1996[99] (Abs)	Diabetes	21
358	FDA-NDA-20-895[101] (Abs) Dinsmore WW et al 1997[102] (Abs) Derry F et a 1997l[103] (Abs) Dinsmore *et al* 1997[102] (Abs) Derry *et al* 1997[103] (Abs)	Spinal cord injury (cord level range T6-L4/5)	27
359	FDA-NDA-20-895[104] (Abs) Abel P *et al* 1997[105] (Abs) Pfizer Study Report[106]	Broad aetiology	111
360	Eardley I *et al* 1997[107] (Abs) Boolell M *et al* 1996[108] (Abs)	No established organic cause	17
361	FDA-NDA-20-895[109] (Abs) Pfizer Study Report[75]	Organic aetiology (excl. spinal cord injury)	254
363	FDA-NDA-20-895[110] (Abs) Cuzin B *et al* 1997[111] (Abs) Pfizer Study Report[76]	Broad aetiology	315
364	FDA-NDA-20-895[112] (Abs) Pfizer Study Report[77]	Broad aetiology	514
367	FDA-NDA-20-895[113] (Abs) Holmgren E *et al* 1998[114] (Abs)	Spinal cord injury	178
369	FDA-NDA-20-895[115] (Abs)	No established organic cause	16
166-301	Pfizer Study Report[80] (Abs)	No established organic cause	10

Phase II Trials

Studies Identified

Eight Phase II trials measured penile rigidity (using a Rigiscan) during visual or vibratory sexual stimulation following oral treatment with sildenafil (Studies 105, 166-301, 350, 351, 357, 358, 360, 369).

Quality of study

These trials were all randomised, double-blind, multicentre, placebo-controlled studies. They were fairly small and most have not been published in full to permit further evaluation. There were small losses to follow up which are not large enough to significantly alter the conclusions.

Evidence of effectiveness

Rigidity of 70% of maximal is considered adequate for sexual intercourse, while rigidity less than 60% is an indication of organic impotence.[116] The initial trials with sildenafil used >80% rigidity as a measure of efficacy, this was later revised to >60% rigidity which was reported in all later trials.

The results of these trials are summarised in Table 7 - Summary of Phase II studies which evaluated penile rigidity with sildenafil treatment followed by visual (or, in study 358, vibratory) sexual stimulation, page 26. Due to the small number of patients studied (171) and the short duration of these trials, limited conclusions can be drawn. In all studies an increased duration of rigidity > 60% was seen with increasing doses of sildenafil. In the 7 studies which calculated a p-value, the response to sildenafil at doses above 25mg was consistently statistically significantly greater than with placebo. The clinical significance of these results is difficult to quantify. The remaining phase II and all phase III studies evaluated the effects of sildenafil on clinical outcomes, i.e. sexual activity, and are much more useful for estimating clinical significance and have involved many more patients.

Table 7 - Summary of Phase II studies which evaluated penile rigidity with sildenafil treatment followed by visual (or, in study 358, vibratory) sexual stimulation

Study ID Location[c]	Design	Cause of ED	Patient Characteristics	Treatments	No. of patients	Duration	Mean duration (min) 60% rigidity of tip of penis	p value vs. placebo	Patients >60% rigidity	Reference/s Date of Study
105 US (MC)	4 period crossover, 1 week washout	Organic & Psychogenic (not spinal cord injury)	Mean age 51-55 ED for >6 months, mean duration not reported	Placebo Sildenafil 25mg Sildenafil 50mg Sildenafil 100mg	54 54 53 53	1 dose 1 dose 1 dose 1 dose	0.06[d] 0.53[d] 0.39[d] 0.95[d]	 p = 0.0002	 Not stated 	FDA-NDA[88] 13/8/96-27/11/96
350 UK(MC)	2 period crossover, 1 week washout	No known organic cause	Mean age - not reported ED for >6 months, mean duration not reported	Placebo tds Sildenafil 25mg tds	16 16	7 days 7 days	7.4 min 36 min	 p = 0.002	 Not stated	FDA-NDA[90] 28/7/93-15/11/93
351 UK(SC)	4 period crossover, Min. 3 day washout	No known organic cause	Mean age 48 (range 36-63) ED for >6 months, mean duration of ED 3.4 yrs	Placebo Sildenafil 10mg Sildenafil 25mg Sildenafil 50mg	12 12 12 12	1 dose 1 dose 1 dose 1 dose	2.9 19 26 27	 p <0.001 	 Not stated 	FDA-NDA[91] Boolell *et al* 1996[70] 24/2/94-30/5/94
357 UK(MC)	3 period crossover, 3-10 day washout	Diabetes	Mean age 50 (range 29-66) ED for >6 months, mean duration of ED 3 yrs (1-14) Diabetes>5 years	Placebo Sildenafil 25mg Sildenafil 50mg	21 21 21	11 days 11 days 11 days	1.3 1.5 (95% CI 0.7 – 2.8)[e] 2.7 2.4 (95% CI 1.3 – 4.4)[e] 4.3 7.2 (95% CI 4.1 – 12.3)[e]	 Not signif. p = 0.002[e]	 Not stated	FDA-NDA[100] Boolell *et al* 1996[99] 2/11/95-11/4/95
358 UK(MC)	2 period crossover 3-7 day washout	Spinal cord injury with ED (cord level range T6-L4/5)	Mean age 33 (range 21-49) ED for >6 months, mean duration of ED 6 years Erectile response to vibrator	 Placebo Sildenafil 50mg	 27 26	 1 dose 1 dose	Median (range) 3 min (2-4)[e] 10 min (0.5 – 72.5)[e]	 p < 0.01	 8% 65%	FDA-NDA[101] Dinsmore *et al* 1997[102] Derry *et al* 1997[103] 13/6/95-29/5/96
360 UK(SC)	2 period crossover, Min. 1 week washout	No known organic cause	Mean age 52 (range 36-70) ED for >6 months, median duration of ED 1.5 years	Placebo Sildenafil 50mg	17 17	1 dose 1 dose	1.1 (95% CI 0.4 – 2.2)[d] 5.9 (95% CI 3.3 – 10.4)[d]	 p =0.001	53% 82%	FDA-NDA [117] Eardley I *et al* 1997[107] Boolell M *et al* 1996[108] 5/9/95-13/2/96
369 UK(SC)	4 period crossover, Min. 1 week washout	No known organic cause	Mean age 55 years ED for >6 months, mean duration of ED 4.5 years	Placebo Sildenafil 100mg Placebo Sildenafil 100mg	16 16 16 16	1 dose 1 dose 1 dose 1 dose	Lasted 2 times as long on sildenafil. No further details given.[d]	p not stated	 Not stated 	FDA-NDA[115] 23/7/96-19/12/96
166-301	3 period crossover Min. 3 day washout	No known organic cause	Age range 32-69 ED for 3 months or more	Placebo Sildenafil 50mg UK-114,542	10 10 10	1 dose 1 dose 1dose	0.8 5.7 (95% CI 1.7-19.4) 5.6 (95% CI 1.8-17.3	 p=0.0084 p=0.0052	 Not stated 	Pfizer (Personal communication) [80] 5/07/95-20/09/95

[c] Countries (SC = single centre, MC = multicentre)
[d] Mean rigidity of the penis (base or tip not specified). Data are reported in minutes but methods section states primary outcome is log transformed duration of 60% rigidity.
[e] Penile base rigidity

Phase II and III trials reporting clinical outcomes

Studies identified

There are 9 phase II trials that evaluate erectile and sexual function (studies 101, 351, 353 , 355, 356, 357, 358, 359, 361) and 7 phase III trials (studies 102, 103, 104, 106, 363, 364, 367). These studies involved approximately 3,772 men with ED of whom 3,003 received sildenafil. Doses ranged between 10mg and 200mg up to once per day for periods of 4 to 26 weeks. Nine trials evaluated fixed doses and 7 were variable dose studies with titration according to response and toleration.

Quality of studies identified

These trials were all randomised, double-blind, multicentre, placebo-controlled studies. Only 3 of these trials have been published in full (1 phase II [351][70] and 2 phase III [102 & 103]),[69] the results from the remaining studies are publicly available as abstracts and/or from the FDA-NDA. The data presented in these latter two sources are not comprehensive enough to allow full evaluation. Pfizer supplied us with protocols and study report synopses for the phase III trials.

Trial design

Methodology

11 were parallel group studies, 4 had a crossover design and 1 had both crossover and parallel group phases.

These trials had several common features. All patients were entered into a 2-4 week treatment-free, run-in period prior to randomisation to allow the collection of baseline data on erectile dysfunction and sexual function. *Generally, one third to one half of all patients enrolled in these trials had successful intercourse during the treatment free run-in period and cannot therefore be considered to be profoundly incapacitated.*

Patients were instructed to take study medication approximately one hour prior to planned sexual activity, but not more than once per day. *Where data are presented 7 – 24% (mean 11%) patients took > 1 dose/day.*[84-86; 105; 110; 112; 113; 115]

Core inclusion and exclusion criteria

The majority of these trials (n = 8) investigated the effects of sildenafil in men with broad spectrum ED, 3 enrolled only men with ED of no established organic cause, 2 men with ED and diabetes, 2 men with ED solely attributable to spinal cord injury (SCI) and 1 ED wholly or substantially organic (excluding SCI). Other than possible restrictions relating to the cause of the ED a number of core inclusion and exclusion criteria were applied in these studies.

Inclusion Criteria

- Men > 18 years
- Erectile dysfunction > 6 months duration
- Heterosexual relationship for > 6 months

Exclusion Criteria

- Anatomical deformities, e.g. severe penile fibrosis
- Other sexual disorders, e.g. hypoactive sexual desire
- Elevated prolactin (3 x ULN) or low free testosterone (20% below LLN)
- Major uncontrolled psychiatric disorders
- History of alcohol or drug abuse
- History of major haematological, renal or hepatic disorder
- Stroke or MI within 6 months
- Cardiac failure, unstable angina, ECG ischaemia or life threatening arrhythmia within 6 months
- BP outside the range 90/50 to 170/100 mmHg
- Active peptic ulcer disease or bleeding disorder
- Clinically significant baseline laboratory abnormality
- Need for anticoagulants, nitrates, androgen or trazodone

- Need for aspirin or NSAIDs and a history of peptic ulcer disease
- Unwillingness to cease using vacuum devices, intracavernosal injection or other therapy for erectile dysfunction
- Other experimental drug use within 3 months
- History of retinitis pigmentosa

Outcomes measured

The International Index of Erectile Function (IIEF) was specifically developed to evaluate sildenafil.[118; 119] (see Appendix 5 - International Index of Erectile Function – IIEF, page 72.)

Primary efficacy endpoints

For the majority of the randomised, double-blind, placebo-controlled studies conducted with sildenafil Questions 3 and 4 of the IIEF were the primary end points:

Question 3	Over the past 4 weeks, when you have attempted sexual intercourse how often were you able to penetrate (enter) your partner?
Question 4	Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you have penetrated (entered) your partner?

Responses to these questions were rated on the following scale:

0 Did not attempt intercourse
1 Almost never or never
2 Most times (much more than half the time)
3 Sometimes (about half the time)
4 A few times (much less than half the time)
5 Almost always or always

(See Appendix 5, page 72. The data obtained from these questions were analysed as continuous data. The means were calculated including the zeros where no attempt at intercourse occurred. This makes the interpretation of the findings difficult as the number of people not attempting intercourse is not given.

Secondary Endpoints

There are several other secondary endpoints reported including:

1. The rest of the **questions from the IIEF** were secondary endpoints.
2. A **global efficacy question** (GEQ): 'Did treatment improve your erections?' was also used. The GEQ was the planned primary endpoint for all these trials. However this was subsequently changed for most studies, on the advice of the licensing authorities, to a secondary endpoint and Q3 and Q4 of the IIEF were made the primary endpoints changing the protocols. The reasoning was that sexual performance rather than erectile function was a more relevant outcome measure.
3. **Event log** – for subjects to record when doses of the drug were taken, attempted intercourse and successful intercourse.
4. **Partner questionnaire** (not compulsory)

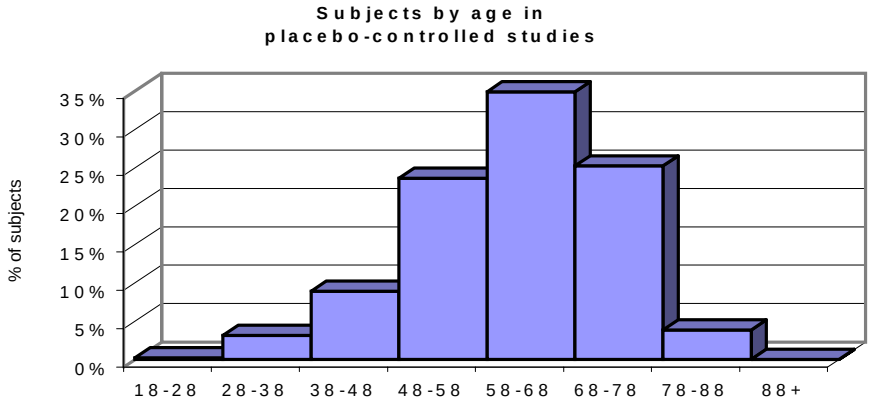
Analysis

Intention to treat analysis was conducted for all outcomes for all randomised patients who had received at least one dose of study drug and undergone at least one post-randomisation assessment. All these analyses were LOCF (last observation carried forward) which can be considered to make placebo (which had a higher withdrawal rate) better than it otherwise would be.

Patient characteristics

Age

The age distribution of patients in the RCTs is shown in the following figure:

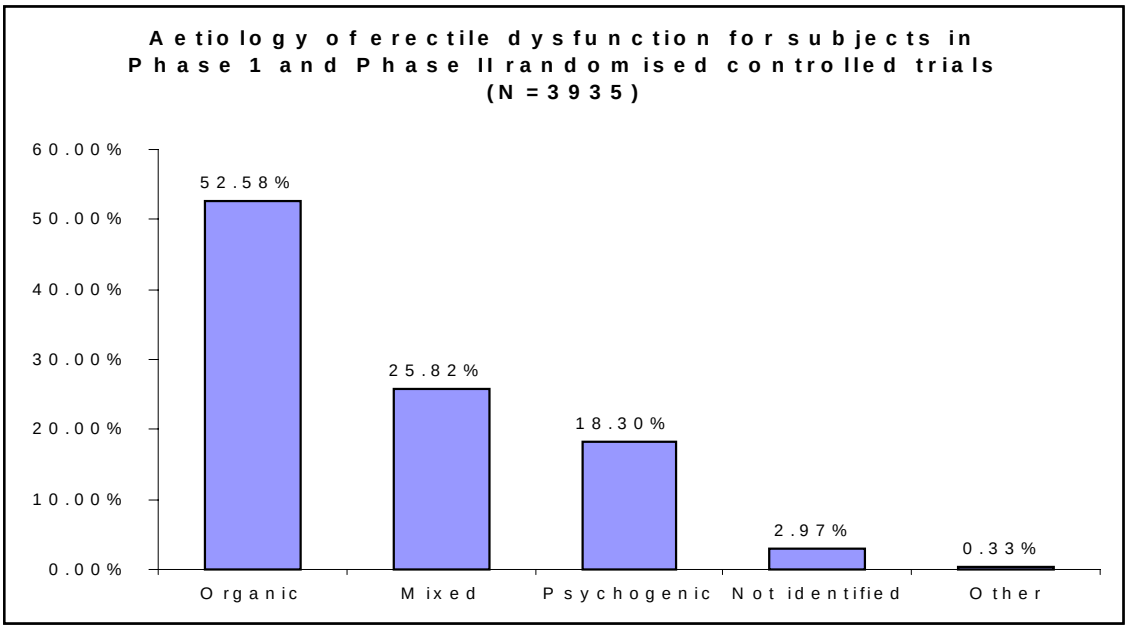


Race

The vast majority of patients (> 95%) involved in the RCTs were Caucasian.

Aetiology of erectile dysfunction

The distribution of the aetiology of ED among the patients included in phase II and phase III randomised controlled trials is shown in the following figure:



Evidence about effectiveness

All of the clinical outcome studies showed a statistically significant treatment effect with sildenafil compared to placebo. The results of these trials are pooled to give an overview of the treatment effects seen.

More than 80% of patients completed these studies, data on patient withdrawals are not consistently reported. Generally, both treatment-related adverse events and insufficient response were responsible for < 5% of withdrawals.

In the 8 dose titration studies there was a strong tendency to migrate to the highest dose available (>50% migrated to 100mg).

Primary endpoints

Frequency of Penetration

Question 3: 'Over the past 4 weeks, when you have attempted sexual intercourse, how often were you able to penetrate (enter) your partner?'

The responses to this question are available for 5 dose titration studies; (103,[85] 104,[86; 87], 359,[105] 363,[111] [110]367[113; 114]) (4 phase III) and 4 fixed dose studies; (101,[83; 115] 102[69; 84], 106,[89] 364,[112]) (3 phase III).

In each of these trials statistically significant improvements, at $p < 0.0001$ level, were seen in question 3 scores with each dose of sildenafil tested compared to placebo.

Increasing improvement was apparent with increasing dose over the range 25–100mg. Only one study evaluated a 5mg dose and only one a 200mg dose. Whilst the response to 5mg sildenafil appears less than with larger doses, the data are too limited to indicate whether an improved response can be expected with 200mg compared to 100mg.

Table 8 - Summary of the mean response to question 3 for each dose of sildenafil

	Fixed dose trials					Dose titration trials
Sildenafil	**5mg**	**25mg**	**50mg**	**100mg**	**200mg**	**25-100mg**
	2.7	3.1	3.5	3.8	3.5	3.7*
Placebo	2.0	2.2	2.2	2.2	2.2	2.1*

**A smaller improvement was apparent with treatment in the trial in men with ED and diabetes. If this trial is removed from the analysis, the mean score to question 3 in the dose titration studies is 3.8 with sildenafil and 2.2 with placebo.*

Without treatment the men with ED evaluated in these studies were generally able, over a 4 week period, to penetrate their partner during sexual intercourse a few times (much less than half the time [score of 2]). With treatment, the frequency of penetration increased to sometimes (about half the time [score of 3]) with 25mg sildenafil towards most times (much more than half the time [score of 4]) with the 100mg dose. The dose titration studies allowed optimal responses to be achieved over the dose range 25-100mg. However the mean score to question 3 seen with sildenafil treatment still remained below the mean score of 4.3 recorded in untreated men without ED.

Maintenance of erection after penetration

Question 4:'Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?'

The responses to this question were presented for the same studies as for question 3.[69; 83; 86; 87; 105; 110-115] The results mirror those for question 3:

In each trial statistically significant, at $p < 0.0001$ level, improvements in patient scores to question 4 were seen with each dose of sildenafil tested compared to placebo.

Increasing improvement was apparent with increasing dose over the range 25 – 100mg. Only one trial evaluated a 5mg dose and only one a 200mg dose. Whilst the response to 5mg was much lower than that seen with higher doses, the data are too limited to evaluate whether an improved response can be expected with 200mg compared to 100mg.

Table 9 - Summary of the mean response to question 4 for each dose of sildenafil

	Fixed dose trials					Dose titration trials
Sildenafil	**5mg**	**25mg**	**50mg**	**100mg**	**200mg**	**25-100mg**
	2.4	3.0	3.2	3.7	3.4	3.5*
Placebo	2.0	2.0	2.0	2.0	1.7	1.8*

**A much smaller improvement was apparent with treatment in the trial in men with ED and diabetes. If this trial is removed from the analysis the mean score to question 4 in the dose titration studies is 3.6 with sildenafil and 1.8 with placebo.*
Study 359 is not included in this summary since the data provided is too limited

Without treatment the men with ED evaluated in these trials were generally able, over a 4 week period, to maintain their erection following intercourse a few times (much less than half the time [score of 2]). With treatment, maintenance of erections increased to sometimes (about half the time [score of 3]) with 25mg sildenafil, towards most times (much more than half the time [score of 4]) with 100mg sildenafil.

In the dose titration studies optimal responses were achieved with the range 25–100mg. As for question 3, the mean score seen with 100mg sildenafil still remained below the mean score of 4.3 recorded in men without ED.

Secondary endpoints

Other IIEF Questions

Where the data are presented, statistically significant ($p<0.01$) dose related increases in the mean scores to the other questions on the IIEF were seen with sildenafil treatment compared to placebo, except for the questions relating to desire where no treatment effect was seen.[69; 86; 105; 110; 111; 114; 115]

General Efficacy Question (GEQ): 'Did treatment improve your erections?'

The data on this outcome were presented for all trials.[69; 70; 83-87; 89; 92-99; 102; 103; 105; 110-112; 115; 120] However the data provided for studies 361[109] & 367[113; 114] were not adequate to allow detailed analysis. In each trial men reported an improvement in their erections with sildenafil treatment compared to placebo. When statistical significance was reported, the improvement seen was significant ($p < 0.001$).

As with responses to questions 3 and 4, a dose response relationship was seen over the dose range 25 – 100mg. Since only one trial evaluated a 200mg dose it is not possible to identify whether a further improvement is seen.

Table 10 - Mean proportion of patients whose erections improved with sildenafil

	Fixed dose trials						Dose titration trials
Sildenafil	**5mg**	**10mg**	**25mg**	**50mg**	**100mg**	**200mg**	**25-100mg**
	48%	60%	65%	75%	82%	80%	72%*
Placebo	28%	37%	26%	26%	24%	25%	18%*
Difference	20%	23%	39%	49%	58%	55%	54%
NNT	5	4.3	2.6	2	1.7	1.8	1.9
**A much smaller improvement was apparent with treatment in the trial in men with ED and diabetes. If this trial is removed from the analysis the proportion of men whose erections improved in the dose titration studies increases to 75% with sildenafil and 20% with placebo.*							

Overall improved erections were seen in 65 – 82% of patients treated with sildenafil 25 – 100mg compared to 18 – 26% treated with placebo.

Event logs – successful intercourse

This outcome was inconsistently presented. Data were available (presented in varying forms) for 6 phase III trials; (102,[69; 84] 103,[69] 104,[86]363,[110; 111] 364,[112]367[113; 114]) (2 fixed dose) and 3 phase II trials; (101,[115] 355,[94] 358[102; 103]) (2 fixed dose).

Only two dose ranging studies (102[69; 84] & 364[112]) presented data for this outcome by dose.[84; 112] The proportion of attempts at intercourse that were successful with sildenafil treatment increased with increasing dose (38% with 25mg increasing to 50% with 100mg compared with 13-24% with placebo).[84; 112] In the dose titration studies, for patients taking placebo 0-25% of attempts were successful compared to 50-60% for patients taking sildenafil 25 – 100mg.[69; 110; 114] The statistical significance of this improvement was only reported for 2 trials, both $p<0.001$.[69; 114] Again, the response in diabetic patients was much smaller; 7.2% placebo and 30% with sildenafil.[86]

The USA package insert for sildenafil states that patient diary records (completed in the clinical trial programme) indicated that sildenafil had no effect on rates of attempted intercourse (about 2 per week), despite increased success rates.[79]

Event log – erections hard enough for intercourse

Six studies presented data on the mean number of erections hard enough for intercourse (i.e. grade 3 or 4)[f] achieved per week; (102,[69] 351,[70] 355,[95] 356,[97] 357,[99] 359[105]).

[f] *Penile responses were graded from 1 to 4 ; 1 increased size but no hardness, 2-increased size & slight increase in hardness but insufficient for intercourse, 3-increased rigidity sufficient for intercourse, 4-full rigid erection*

In each study an improvement in the number of grade 3 and 4 erections was seen with sildenafil treatment.

Table 11 – Mean number of grade 3 and 4 erections/week

Study	Mean No. grade 3 & 4 erections/week			Statistical significance
	Sildenafil		Placebo	
	Dose			
102 Goldstein *et al*[69]	25mg	1.1	0.8	p < 0.001
	50mg	1.6		
	100mg	1.6		
351 Boolell *et al*[70]	25mg	1.9	0.6	
355 Eardley *et al*[95]	25-100mg	4.6	1.4	p < 0.001
356 Bailey *et al*[97]	10-100mg	1.5	0.6	
357 Boolell *et al*[99]	25mg	1.7	0.7	p=0.0001
	50mg	1.9		p=0.002
359 Abel *et al*[105]	25-100mg	1.7	0.6	p < 0.001

With the exception of study 355[95] where higher placebo and treatment responses were seen, 0.6 - 0.8 grade 3 and 4 erections were achieved/week with placebo compared to 1.1 – 1.9 with sildenafil 25-100mg. A dose response relationship was apparent.

Partners' Questionnaire

Most of the studies provided partners with an optional questionnaire. No details of the questions asked are provided in the abstracts. Results are presented for 7 trials; 101,[115] 102,[69] 103,[69] 104,[87] 353,[92] 363,[111] 364.[112] Response rates ranged from 20% to 94% but tended to be below 50%. Due to the limited data provided, detailed analysis of this variable is not possible. Overall the responses to the partners questionnaire corroborated the improvement in erections, ability to penetrate and maintain erections reported by patients. Generally, increasing partner satisfaction was seen with increasing sildenafil dose (10 – 100mg).

Quality of Life

A number of the clinical outcome studies included a quality of life questionnaire in the study design. None of the study reports have presented comprehensive data on this questionnaire. The most detailed data are provided for study 103.[85] The published report for this study does not present quality of life outcomes but the FDA report identifies that 'several quality of life questions demonstrated a nominally high statistically significant treatment effect – health compared to a year ago, satisfaction with relationship, impact of erectile problems – but the treatment effect size was, in each case, small'.[85] Again, the FDA report identifies statistically significant but small quality of life treatment effects in 3 other studies; 102,[84] 364,[112] 104.[86]

Data from Pfizer indicate that 940 patients with ED of broad spectrum aetiology enrolled in 3 European pre-registration clinical trials completed a battery of generic quality of life questionnaires at baseline and after 12 weeks of treatment with sildenafil 25 – 100mg or matching placebo. The results of this analysis will be presented during 1998. The aim is to produce a universally adopted QoL instrument for men with ED.[121]

Adverse effects

Sildenafil has been evaluated in approximately 4,500 patients, of whom 560 received treatment for at least 1 year. In dose titration clinical trials adverse events were reported by approximately 60% and 40% of patients on sildenafil and placebo respectively but were responsible for drug withdrawal in only 2.5% and 2.3% respectively.[79] A further 1.9% withdrew due to adverse events during open label treatment.[122] Adverse events were predominantly transient, mild or moderate in nature and dose related with approximately 2/3 of all reports classified as mild.[123] The majority of adverse events associated with sildenafil are related to vasodilation (including headache, flushing, nasal congestion),

gastrointestinal events (dyspepsia) and visual effects (abnormal vision). All these events reflect the known pharmacological properties of sildenafil.[123]

Table 12 - Summary of adverse events reported in >2% of patients treated[117; 120]

Adverse Event	Flexible dose studies		Open label studies up to 1 year
	Sildenafil n = 734	Placebo n = 725	Sildenafil n = 2199
Headache	16%	4%	10%
Flushing	10%	1%	9%
Dyspepsia	7%	2%	6%
Nasal congestion	4%	2%	NR
Urinary Tract Infection	3%	2%	NR
Abnormal vision	3%	0%	2%
Diarrhoea	3%	1%	NR
Dizziness	2%	1%	NR
Rash	2%	1%	NR
Respiratory Tract Infection	equally common	equally common	6%
Withdrawals due to AE	2.5%	2.3%	2%

NR – not reported

A similar range of adverse events were reported in the fixed dose trials.

Generally the overall incidence of treatment related adverse events and the incidences of the most commonly reported adverse events increased as the dose of sildenafil increased. In particular, at the 100mg dose the incidence of dyspepsia (17%) and abnormal vision (11%) was higher than with lower doses. The incidence of adverse events has been modelled estimating an incidence of abnormal vision of 40%, gastrointestinal events of 15% and vascular events of 25% with a 200mg dose.[124] Small clinical studies explored doses up to 800mg. Whilst higher incidences of events were seen than at lower doses no new phenomena developed. The adverse events seen were rarely serious.[125]

No cases of priapism were reported in any of the sildenafil studies. One healthy volunteer given 600mg reported an erection lasting 5 hours.[126] No other reports of prolonged erection are given.

Sperm

No effect on sperm motility or morphology after single oral doses of 100mg to healthy volunteers has been seen.[127]

Visual

Clinical trials have identified that sildenafil (particularly at high doses, i.e. >100mg) can have adverse effects on vision, reported as light sensitivity and a mild, transient (lasting from a few minutes to a few hours) change in colour discrimination in the blue-green range (3% 25mg, 11% 50-100mg, 58% > 100mg). These changes are believed to result from inhibition of PDE6 by sildenafil. The PDE6 enzyme is present in the retina and involved in phototransduction.[128]

No effect on other objective measures of visual function, e.g. visual acuity, contrast sensitivity and intraocular pressure have been reported with sildenafil. The visual disturbance seen is considered not to pose a risk to men operating motor vehicles or other heavy equipment.[125]

The American Academy of Ophthalmology (AAO) has expressed concerns regarding the visual side effects seen with sildenafil.[129; 130] In particular they are concerned about possible permanent changes in vision and use in patients with retinal eye diseases, since data on use in these patients are limited. Pfizer are quoted as being 'confident that the blue vision effect is transient and has no lasting effects on the eye or the retina', however, the AAO indicate that long term studies are required to establish whether sildenafil is associated with any permanent changes in vision. These are not yet available.

Pfizer advise use with caution in patients with retinal eye conditions.[128; 130]

Cardiovascular

PDE5 occurs in the systemic vasculature. Cardiovascular adverse events with sildenafil have been studied in detail.

The pooled safety data from 18 double-blind, placebo-controlled trials (2722 patients received sildenafil 25 – 100mg and 1552 placebo for up to 6 months) gives an overall incidence of cardiovascular events (other than flushing) of 3.0% with sildenafil and 3.5% with placebo. Tolerability was not affected by concomitant antihypertensive use. A comparable incidence rate (per 100 man years of treatment) was also seen with sildenafil and placebo for serious cardiovascular events. Serious cardiovascular events included myocardial infarction (MI), angina and coronary artery disorder.[123]

Table 13 - Incidence of Serious cardiovascular events and MI in patients treated with sildenafil or placebo in Phase II/III studies[123]

Studies	**Incidence (per 100 men years of treatment) [95% CI]**	
Placebo controlled trials:	**Sildenafil**	**Placebo**
Serious cardiovascular events	4.1 [2.7 – 5.5]	5.7 [3.3 – 8.2]
MI	1.7 [0.8 – 2.6]	1.4 [0.2 – 2.6]
Open label extensions: *(2199 patients received sildenafil for up to 1 year)*		
Serious cardiovascular events	3.5 [2.3 – 4.7]	
MI	1.0 [0.3 – 1.6]	

From the double-blind, placebo-controlled trials no clinically significant changes in blood pressure, heart rate or ECG were seen with sildenafil treatment. A peak reduction in blood pressure of 8/6mmHg accompanied by an increase in heart rate was seen around the time of peak plasma concentration.[125]

Sildenafil had no direct effect on platelet aggregation.[79]

Withdrawal

The FDA NDA identifies that withdrawal effects have not been formally studied.

Priapism

A small number of cases of priapism have been reported in post-marketing surveillance since the launch of sildenafil in the U.S.A. Further details are not available at the current time. It is not possible to comment, therefore, on the significance of this. Pfizer is reviewing the prescribing guidance to consider whether to include a warning. (Pfizer, personal communication, 10th August 1998)

Deaths reported during trials

The FDA report indicates that 8 patients out of a total of 4,500 treated with sildenafil in clinical trials died whilst taking the study drug or within 30 days of treatment. Six of these deaths were related to cardiovascular causes. In all cases it was plausible that the event was not related to study drug.[125; 131]

All deaths post-marketing

As at August 24 1998, the latest post-marketing surveillance information available from the FDA or Pfizer gives information to the end of July 1998. From the end of March to July 1998 there were 123 deaths reported to the FDA among men using sildenafil.[132] They have occurred in the context of over 3.6 million prescriptions issued and are not thought to be indicate an excess of deaths with the use of sildenafil. (see Appendix 6 - FDA Postmarketing Surveillance Report, page 78, for full report).

Twelve deaths concerned non-U.S. patients, 30 reports were unverifiable, 12 reports could not confirm the use of sildenafil. The gender was specified for 66 deaths, all were men. Details are given for the remaining 69 deaths. **Cause of death:**

- Unknown or unspecified 21
- Stroke 2
- Myocardial infarction 21
- Cardiac arrest 17
- Other cardiac event 8

The **average age**, where specified, was **64 years** (median 64, range 29-87). Of 31 **doses** reported, 26 had taken **50mg,** 3 had taken **100mg**, and 2 had been prescribed **50-100mg**. Fifty-one of the 69 patients (74%) had one or more risk factors reported for coronary artery disease. Three further patients had severe coronary artery disease detected at autopsy.

Open label extension studies

Ten long term (usually 52 week) open label follow-up studies have been undertaken with sildenafil. Outcome data are only provided for two of these studies.[133-135] The data presented is very limited and has several numerical inconsistencies which do not allow evaluation. The only consistent feature is that 90% of patients expressed satisfaction with treatment at the end of the study.

Special patient groups

Diabetics

Two studies evaluated the effects of sildenafil in diabetic men with ED. The results of these studies have only been published in abstract form, supplemented by data provided in the FDA NDA.[86; 87; 99]

A double-blind, randomised, placebo-controlled crossover pilot study in 21 men (mean age 50) with diabetes and ED. The first phase measured penile rigidity following a single dose of sildenafil (25mg and 50mg) and placebo. The data presented on this outcome do not identify the proportion of men who achieved a penile base rigidity > 60% with each treatment. In the second phase patients received sildenafil (25mg and 50mg) and placebo once daily for 10 days (no further details given). Improved erections were reported by 10% of patients with placebo, 48% with 25mg ($p < 0.005$) and 52% with 50mg ($p < 0.005$) sildenafil respectively. Additionally the mean number of erections hard enough for intercourse (grade 3 and 4) were 0.7, 1.7 and 1.9 with placebo and sildenafil 25mg and 50mg respectively ($p < 0.005$).[99]

Study 104 was a phase III, 12 week, randomised, double-blind, fixed dose, placebo-controlled, parallel-group study conducted by 19 investigators in the USA in 268 men with ED and diabetes mellitus (18.7% type I, 81.3% type II). Patients had a mean age of 57, mean duration of ED of 5-6 years and mean duration of diabetes of 12.1 years. 136 patients were randomised to treatment with sildenafil 50mg (dose titration up to 100mg or down to 25mg was permitted based on efficacy and tolerability) and 132 to placebo.

Baseline sexual performance data indicated that only 1/5th of patients had erections sufficient for intercourse during the 4 week treatment free run-in period.

At the first opportunity more than 75% of patients migrated to the 100mg dose. 7% of patients took > 1 dose/day. After 12 weeks treatment statistically significant improvements ($p < 0.0001$) in the scores to question 3 (3.2 vs. 2.0) and question 4 (2.9 vs. 1.6) of the IIEF were seen with sildenafil compared to placebo. The general efficacy question indicated that significantly more patients treated with sildenafil had improved erections; 57% vs. 10%, $p < 0.001$. Successful intercourse was reported by 30% and 7.2% of sildenafil and placebo treated patients respectively (p value not given). Whilst a beneficial effect was apparent with sildenafil in these outcomes, the improvements seen were much smaller than those recorded with treatment in men with ED of broad aetiology.[86; 87]

An abstract report[136] has summarised the pooled efficacy data on sildenafil in the men with ED due to diabetes mellitus enrolled in 9 double-blind, placebo-controlled trials; 101, 102, 103, 104, 106, 359, 361, 363, 364. A total of 633 men (mean age 57) with ED and diabetes (21% type I; 79% type II) were included in the analysis; 388 received sildenafil (5 – 200mg) and 245 placebo for 6 – 26 weeks.

At endpoint (varied according to trial design) statistically significant improvements ($p < 0.001$) in the scores to question 3 (2.86 vs. 1.85) and question 4 (2.66 vs. 1.54) and in the proportion of patients with improved erections 59% vs. 15% were recorded with sildenafil compared to placebo. Again the improvements seen were much smaller than those recorded with treatment in men with ED of broad aetiology.[136]

Spinal cord injury

Two studies evaluated the effects of sildenafil in men with ED solely attributable to SCI but still evidencing reflex activity. These have both been published in abstract/poster form with supplemental data in the FDA NDA.

An initial study[102; 103] had two phases. The first phase was a crossover pilot study which looked at the effects of sildenafil on penile rigidity in 27 men (mean age 33 years) with ED solely attributable to SCI (cord level range T6 – L4/5). A single dose of sildenafil 50mg produced a penile base rigidity > 60% in 65% of patients compared to 8% of patients on placebo ($p < 0.01$). The second phase randomised patients to double-blind treatment with sildenafil 50mg ($n = 12$) or placebo ($n = 14$) for 28 days. The GEQ administered after this time identified a statistically significant ($p < 0.01$) improvement in

erections with sildenafil compared to placebo; 75% vs. 7%. The FDA report states that the proportion of successful intercourse attempts was 67% for those patients on sildenafil and 38% for those on placebo.[102; 103]

The second trial was a randomised, double-blind, placebo-controlled, crossover study in 178 men (mean age 38) with ED (mean duration 10.5 years) solely attributable to SCI (cord level range not specified).[113; 114] Patients were randomised to 6 weeks treatment with sildenafil 50mg (adjusted between 25 – 100mg according to response) or placebo, and then crossed over after a 2 week washout period to the alternative treatment for 6 weeks. 94% of patients completed the two treatment phases, with 74% expressing a preference for sildenafil. At the end of 6 weeks treatment 4.6%, 36.8% and 58.6% were receiving sildenafil 25mg, 50mg and 100mg respectively. Statistically significant ($p < 0.0001$) improvements in the scores for question 3 (2.2 vs. 3.8) and question 4 (1.7 vs. 3.6) were seen with sildenafil compared to placebo. 83% of patients on sildenafil and 12% on placebo reported improved erections ($p < 0.0001$) with a median of 55% of successful attempts at sexual intercourse with sildenafil compared to 0% with placebo ($p < 0.0001$). Approximately 50% of partners responded on the partners questionnaire. Statistically significant treatment effects were recorded relating to the patients' erections and satisfaction of sexual intercourse. Further outcome data are not given.[113; 114]

From these two trials, sildenafil appears to show comparable efficacy in patients with ED solely attributable to SCI (but with intact spinal cord-mediated reflexes) to patients with ED of broad spectrum aetiology.

Radical prostatectomy

Four percent of patients enrolled in phase II & III clinical trials had ED as a result of radical prostatectomy. A subgroup analysis of these patients appear to show lower efficacy with sildenafil, only 40-50% achieving improved erections (personal communications, Pfizer June 1998).[79]

Ethnic groups

No analysis has been performed on effectiveness according to race (only ≈ 6% of patients in clinical trials were non-caucasian).

Elderly

A meta-analysis has been conducted by Pfizer of 8 double-blind, placebo-controlled, fixed or flexible dose phase II/III studies.[137] The analysis considered efficacy in both elderly (≥ 65 years old, n = 742) and non-elderly men (n = 2240). A statistically significant treatment response of similar magnitude ($p < 0.0001$) was seen irrespective of age:

Q3 – ability to achieve an erection, mean scores were 3.6 vs. 2.2 in men < 65 and 3.1 vs. 1.8 in men ≥ 65 for sildenafil and placebo respectively.

Q4 – ability to maintain an erection, mean scores were 3.4 vs. 1.9 in men < 65 and 3.0 vs. 1.6 in men ≥ 65 for sildenafil and placebo respectively.

GEQ – improved erections were reported by 75% vs. 23% of men < 65 and 67% vs. 17% of men ≥ 65 years for sildenafil and placebo respectively.[137]

Drug interactions

Sildenafil is metabolised principally by the cytochrome P450 isoform 3A4:

CYP3A4 inhibitors

CYP3A4 inhibitors such as cimetidine, erythromycin, ketoconazole and itraconazole, can be expected to increase sildenafil levels by reducing clearance. In vivo studies have identified only a small increase with cimetidine, but much larger increases are seen with the other CYP P450 3A4 inhibitors. When patients are co-administered erythromycin, ketoconazole and itraconazole due to the increased potential for adverse effects, prescribers are advised to use a low starting dose of sildenafil or to reduce the sildenafil dose in patients established on treatment.[79]

CYP3A4 inducers

CYP3A4 inducers such as rifampicin can be anticipated to decrease plasma levels of sildenafil. Higher doses may therefore be required in these patients.[79] Sildenafil itself is a weak inhibitor of CYP450, but no clinically significant interactions have been seen.[79]

Nitrates

A substantial drop in blood pressure (max -29/52mmHg) for more than 6 hours and a substantial increase in heart rate (max. approx. 12 bpm) for approximately 3 hours has been seen when sildenafil is administered to patients on nitrates.[138] **Combined use is therefore contra-indicated**.[79] In the USA all A&E departments have been informed of this serious interaction both to increase their awareness in (1) reviewing admitted patients who may have taken both a nitrate and sildenafil at home and (2) in treating patients presenting with angina. [139]

Antiplatelets.

A number of studies investigated the effects of sildenafil on platelet aggregation in healthy men given other treatments. It appears that sildenafil has no direct effect on platelet aggregation. However, administration of sildenafil in combination with:

- *Sodium nitroprusside*, a donor of nitric oxide, enhances platelet aggregation.[140]
- *Low dose aspirin*, is likely to prolong bleeding time in some individuals.[141]

No interaction has been seen with sildenafil and alcohol, warfarin, tolbutamide and amlodipine.[79]

Comparison with alprostadil

Sildenafil has not been directly compared with alprostadil in any formulation. Comparative trials are due to commence in 1998.

There are key differences in the mechanism of action of these two drugs: Alprostadil is a vasodilator which acts to relax smooth muscle directly. Intracavernosal or transurethral administration produces erections in the absence of sexual arousal. Vasodilator therapy carries the risk of prolonged erection and priapism requiring medical reversal.

Sildenafil enhances the effects of nitric oxide within the corpus cavernosum leading to enhanced erections. Nitric oxide is released in response to sexual stimulation. Sildenafil therefore enables an erection to develop rather than producing an erection. It is ineffective in the absence of arousal.

Due to their different mechanisms of action, it is anticipated that vasodilator therapy may be effective in some patients in whom sildenafil is ineffective and vice versa.[142] This has yet to be addressed in any trial. Combined therapy has also not been studied and is therefore not recommended.

It is anticipated that neither treatment would probably be effective in men with ED caused by severe arterial insufficiency, loss of trabecular smooth muscle, or incompressible cavernosal veins.[142]

The studies which have been conducted with alprostadil and sildenafil are not directly comparable, because of differences in study subjects, assessments of efficacy and duration. Table 19 - Controlled trials with alprostadil, page 51, summarises the key trials with intracavernosal and transurethral alprostadil.

Future Developments

A number of other products are in active development for the treatment of ED. Two oral treatments and one intracavernosal therapy are in the late stages of development:

- oral phentolamine (Vasomax) has been submitted to the US FDA with the hope of launching at the end of 1998. It was launched in Mexico (its first market) in June 1998.
- sublingual apomorphine is in phase III trials, licence submission is planned for early 1999.
- intracavernosal vasoactive intestinal peptide and phentolamine (Invicorp II) has been submitted for a UK produce licence. It is currently available on a named patient basis.

Other anticipated treatments represent re-formulations of alprostadil. Harvard Scientific are developing a liquid formulation of alprostadil which is squirted down the urethra from a soft silicone nipple. NexMed is developing a cream formulation of alprostadil (Alprox –TD) which is applied to the glans of the penis. Both of these products are currently undergoing phase II trials. Pfizer is reputed to be investigating the development of a fast-dissolving formulation of sildenafil.(Scrip 2332/33:24)

Implications for NHS

Prescribing in primary care

> *"… the primary diagnosis and treatment of ED can be undertaken safely and more efficiently in the primary care sector."*
>
> British Association of Urological Surgeons{Fletcher & Kirby 1998 ID: 201S}

Safety and effectiveness

There are two important considerations to bear in mind, from a safety and effectiveness perspective, when deciding where is the most appropriate place for prescribing a treatment: the nature of the treatment itself and the degree of experience and expertise necessary for diagnosing and assessing the disease or condition to be treated. Currently most treatments for erectile dysfunction are initiated in secondary care. This has been to a large extent because of the nature of the treatments and the need to train patients in how to use them.

The nature of the treatment

The relative safety and ease of use of sildenafil suggests that it is entirely appropriate for it to be prescribed by primary care physicians. We have talked to a considerable number of urologists, general practitioners, and pharmacists and the consensus is that, from a clinical perspective, there is nothing special about the drug that would suggest that it needs to be prescribed by specialists. The major contraindication for sildenafil is its use in patients taking nitrates. It has been suggested that a patients' primary care physician who is most likely to be aware of the patients' routine medication and general cardiovascular status. It is also the GP who is frequently in the best position to be aware of the family situation and other social, medical or psychological factors that might be relevant in assessing or advising a man with ED who wishes to start on oral treatment.

The assessment of erectile dysfunction

The assessment of a patient with ED is also thought to be well within the competencies of a general practitioner. Routinely, men with ED presenting to secondary care are diagnosed on history, clinical examination and some basic diagnostic tests (e.g. for diabetes). Other investigations are rarely necessary and are usually indicated by some aspect of the history or physical examination (e.g. testosterone levels, thyroid function, prolactin levels). The fact that there is no obvious organic cause does not alter the fundamental assessment undertaken currently.

Cost

There are no obvious reasons why prescribing in primary care should cost more per man treated than prescribing in secondary care. Although some people have argued for restricting prescribing to secondary care which would act as a bottle-neck for access to treatment and thereby reduce the overall cost to the NHS, even though the unit cost of treatment in secondary care would be higher than in primary care.

The general opinion as expressed to us is in agreement with the view of the British Association of Urological Surgeons as expressed in a letter to the Rt. Hon Alan Milburn MP, Minister of State (see :

> *"the proposal … that the new treatment for erectile dysfunction, Viagra, should be prescribe only after a patient has been seen by a specialist … is an impractical and undesirable recommendation.*
>
> *"In the majority of patients, the diagnosis of ED and its most likely underlying cause can easily be made in primary care through the following of straightforward protocols. From a clinical perspective, specialist referral is only indicated when there is confusion about the diagnosis, underlying cause, or when the patient has failed to respond to first-line treatment.*
>
> *"It appears that the requirement for secondary case referral is being set merely to create a barrier in providing treatment to men with ED in an attempt to control costs rather than on any clinical grounds. This appears to us to be an inappropriate way to utilise the time and skill of the already stretched resources of urologists and*

other specialists in the health service. Furthermore, it has serious implications for the provision of urological services across a wide range of conditions….

"In conclusion, with these new, non-invasive techniques for treating ED (i.e. Viagra and MUSE) the primary diagnosis and treatment of ED can be undertaken safely and more efficiently in the primary care sector."[131]

Both urologists and GPs consulted have expressed concern about the potential increased workload (and costs) the licensing of sildenafil will bring. Urology services are not in a position to cope with demand if all cases are referred from primary care. From the epidemiological evidence showing unmet need and the extensive media interest about sildenafil, we anticipate that there is going to be a considerable demand in terms of time and money on the NHS. This potential demand is such that it is unlikely to be able to be absorbed within the current system without serious disruption or damage unless specific strategies to cope with it are put into place.

Use outside product licence

Therapeutic effects in healthy men have not been formally evaluated. Normal volunteer studies, undertaken to evaluate the pharmacokinetics, pharmacodynamics and tolerability of sildenafil, in small groups of men suggest that an increase in number or duration of erection may occur in men without ED. However these data are very limited,[126] and Pfizer have not done any trials looking at the therapeutic effect in men without ED. It is anticipated that there may be demand for the drug in men with perceived reduced sexual functioning ("erectile dysphoria"), in the hope of 'improving performance'. There is concern that such men could become 'psychologically hooked' on the drug.

There is no evidence that sildenafil has any benefit for men with other sexual dysfunctions such as hypoactive sexual desire or premature ejaculation.

Sildenafil is being tested on women in planned clinical trials. It is not currently indicated for use in women.

8 COST-UTILITY ANALYSIS OF SILDENAFIL TREATMENT FOR ERECTILE DYSFUNCTION

There is a great deal of uncertainty surrounding the assumptions used to calculate the cost per QALY of treating erectile dysfunction with sildenafil. Our best estimate is that the cost per QALY is around:

£7,000 per additional QALY gained

Benefits and disbenefits

Table 14 illustrates the possible benefits and adverse consequences of the use of sildenafil in men with erectile dysfunction. In addition to these possible benefits and disbenefits, there may be increased detection of organic disease in men requesting sildenafil treatment because erectile dysfunction may be the presenting symptom of an underlying disease. Treatment of detected underlying disease will be associated with increased treatment costs for the NHS, yet improved detection and management of disease will yield substantial future savings to the NHS and improvements to individuals' length and quality of life.

Table 14 – Benefits and disbenefits

Possible benefits	*Possible disbenefits*
Attaining erection sufficient for intercourse Confidence in ability to attain erection Improved self-esteem Improved sexual relationship with partner Improved overall relationship with partner Partner satisfaction from improved relationship	Distress of non-responders Problem of heightened expectations in both non-responders and in responders where physical sexual functioning was being set out as cause of general QoL/relationship problems Substantial change to relationship basis can have adverse effect on man and/or partner

Studies looking at the cost-utility of using sildenafil to treat erectile dysfunction

Only one trial reports on the impact of sildenafil treatment on patients' quality of life.[143] Participants completed a battery of quality of life instruments, however these did not include a multi-attribute health status measure which would enable quality of life impact to be expressed in terms of QALYs (quality-adjusted life years).[144] As such, there is currently no available data which allows us to directly calculate the cost-utility of sildenafil treatment. This section attempts to construct cost-utility estimates from available data on the impact of erectile dysfunction on quality of life parameters, the above findings on the clinical effectiveness of sildenafil, and current cost estimates (Pfizer, personal communication August 1998). Calculations assume primary care prescribing.

Quality of life assessment in urology

The importance of quality of life outcomes in urology was highlighted by a US study which showed that men were willing to trade survival for maintenance of sexual function.[145] Yet until recently, there had been relatively little research carried out on the assessment of health related quality of life of patients with urological conditions. The last few years have seen the development of a substantial body of research regarding health-related quality of life in patients with genitourinary malignancies (especially prostate cancer) and benign prostatic hyperplasia (BPH). This has included the development and validation of disease-specific quality of life instruments, as well as the use of generic quality of life questionnaires such as the Nottingham Health Profile, SF-36 and EQ-5D (formerly called the EuroQoL).[146; 147] In contrast, there remains little research examining health related quality of life in patients with other urological conditions, such as incontinence and sexual dysfunction. Incontinence and erectile dysfunction are typically assessed by traditional outcome measures i.e. questions on degree and frequency of incontinence or on frequency and satisfaction of sexual activity. However, assessing the impact of these conditions on quality of life also requires subjective measures of severity.[146]

Quality of life impact of erectile dysfunction

Ofman[148] provides a detailed discussion of the possible quality of life impact of male erectile dysfunction and highlights the shortcomings of current attempts at its measurement:

> "*Possibly because of the difficulty of assessing the complex question of sexual functioning in the context of quality of life, it is usually measured as a sub-category of physical functioning.. Often, no clear definitions of what constitutes dysfunction are given… [and questions do not] take into account the possibility that even if no intercourse occurs, there may be erectile functioning, sexual desire and other sexual behaviour. The systematic assessment of sexual functioning would require a structured interview or questionnaire in which the following dimensions were evaluated: sexual interest (thoughts about sex, wish for sexual activity, auto-eroticism), sexual arousal (sensation of feeling sexually aroused, occurrence of erection, volume and rigidity of the erection both in situations with partner and without), orgasm (premature ejaculation, difficulty ejaculating, sensation), pain & discomfort during or after sexual activity, body image, and masculine self-image.*"[148]

A recent review of studies addressing quality of life effects of erectile dysfunction notes that the lack of high quality information in this field could be expected given that ED was until recently a relatively little-studied disease with few treatments and scarce epidemiological data.[121] The review summarises the findings of both observational studies and intervention studies and sets out the case for the development of a new disease-specific quality of life instrument for erectile dysfunction.

Several observational studies have found a negative association between (severity of) erectile dysfunction and general quality of life scores.[14; 16; 149] The Massachusetts Male Aging Study[13] found a

significant positive association between erectile dysfunction and both depression and anger expression or suppression. The absence of control groups in such studies makes interpretation of these findings difficult, and some authors note that such associations may well be due to the influence of co-morbid disease and/or of uncertain causality.[16 13]

The impact of erectile dysfunction on health related quality of life has been assessed in several recent clinical trials of alprostadil injections, MUSE and sildenafil.[16; 58; 143; 150; 151] An immediate problem for any attempt to summarise these findings in a comparative format is that each trial used a different combination of generic and disease-specific quality of life instruments.

Quality of life and alprostadil injections

Two studies of men on alprostadil injection therapy show significant improvements in sexual functioning and in mental health and self-esteem dimensions of the Duke Health Profile;[12; 58] however the small number of participants in one study[12] and lack of control group in either make interpretation of these findings difficult.

Quality of life and transurethral alprostadil

The results of two placebo-controlled trials of transurethral alprostadil (MUSE) including quality of life instruments are currently available only in abstract form.[150; 151] These found significant improvements in emotional well-being and in relationship with partner for MUSE-responders, although these results should be treated with caution until publication allows the quality of the trials to be assessed.

Quality of life and sildenafil

The results of a 'battery of quality of life instruments' completed by 940 men participating in three randomised placebo-controlled European pre-registration trials of sildenafil are also available, so far, only in abstract form.[143] The study reports quality of life scores for men (mean age 55.3 years, mean duration of ED 4.8 years) with broad-spectrum aetiology ED (281 known organic cause, 273 psychogenic cause, 375 mixed, 11 other) at baseline and at 12 weeks; using SF-12 mental and physical health summaries; Psychological General Well-being Index (PGWBI); Rosenberg Self Esteem Scale; Medical Outcomes Study Family Interaction Survey; Impact of Erectile Problems Scale (IEPS); and questions on satisfaction with relationship with partner and general health compared to three months ago. Those receiving sildenafil treatment showed significant improvement at 12 weeks compared to placebo on SF-12 mental health summary, the positive well-being, self-control and depression dimensions of PGWBI, IEPS and questions on satisfaction with relationship with partner and general health (mean improvement on these scales 0 to 30% compared to -4 to 7% for placebo). The placebo group showed a significant improvement over sildenafil on SF-12 physical health summary score, other instruments showed no significant effect. The authors conclude that sildenafil treatment results in significant improvements in key quality of life parameters, although assessment of these findings awaits the availability of the full results.

Cost-utility analysis

Whilst the IIEF is now accepted as a measure of clinical effectiveness in erectile dysfunction treatment, there exists no comparable single measure to capture the impact of erectile dysfunction on patients' quality of life. Assessments of the impact of ED on health related quality of life have used a variety of generic and disease-specific measures, however generic measures used thus far do not include utility scales which can be used to construct QALYs.

Erectile dysfunction is a non-fatal condition and treatment has no obvious impact on life expectancy, so the benefits of any treatment for this condition in QALY terms will be expressed solely in terms of improvements in patients' quality of life.

Utility values associated with erectile dysfunction

Three studies have estimated utility values for erectile dysfunction, all in the context of prostate cancer: two decision analysis studies concerning treatment[152] and screening[153] strategies for localised prostate cancer include expert-determined utility values for impotence and other adverse effects of treatment; and a recent observational study available in abstract form estimates utilities from patients undergoing biopsy for prostate cancer.[154] The studies estimate utility values for major adverse effects of prostate cancer treatment on a 0-1 scale (where 0 represents a state of health equivalent to death and 1 represents a state of health equivalent to full health); results are shown below.

Table 8 - Utility values associated with erectile dysfunction

Study	Fleming et al.[152]	Krahn et al.[153]	Saigal et al.[154]
Method	Utility values assigned to each health state outcome based on **consensus of clinicians** involved in outcomes research and prostate cancer treatment	Utilities for chronic health states were elicited from a group of 10 **physicians** by constructing scenarios describing conditions and using "Gambler" automated tool using time trade-off method	**Patient** preferences measured using U-Titer-II computer-based instrument using time trade-off technique. Definitions: complete ED; moderate stress incontinence; moderate rectal symptoms
Utility values:			
Impotence	0.95 (0.85, 0.90, 1.0)	Partial: 0.92 Complete: 0.85 (0.75, 0.95)	0.67 (mean value, standard deviation 0.38)
Incontinence	0.70 (0.55, 0.85, 1.0)	Partial: 0.81 (0.71, 0.91) Complete: 0.61 (0.51, 0.71)	0.77 (mean value, standard deviation 0.35)
Bowel dysfunction	0.85 (0.55, 0.70, 1.0)	n/a	0.55 (mean value, standard deviation 0.44)

Figures in parentheses for Fleming & Krahn studies show values used in sensitivity analysis

Whilst these valuations are specific to erectile dysfunction, they relate to interested parties (clinicians and patients) whose valuations may be expected to overstate those of the general public. Utility values given above provide a range of estimates of the impact of erectile dysfunction on health related quality of life, against which estimates derived from standard generic instruments can be checked.

Estimating utility values for erectile dysfunction

In order to generate a single utility estimate for the reduced quality of life of men with erectile dysfunction it is necessary to hypothetically place this condition on a generic health-related quality of life descriptive instrument.

This is attempted using the IHQL and EQ-5D generic indices (see Appendix 7 – IHQL, page 80 and

Appendix 8 - EQ-5D (EuroQoL), page 81). An overriding problem in this translation is the exclusion of sexual functioning from the main generic health-related quality of life scales currently used in the construction of QALYs. As such, the following calculations should be taken as wide estimates of the quality of life changes associated with the use of sildenafil.

The appropriate utility value to be used depends on the precise translation of problems of sexual functioning and its impact on relationships and overall quality of life onto instruments which explicitly include neither sexual function nor relationships. In both the measures used here, we assume that erectile dysfunction affects quality of life only in the dimension of emotional distress and anxiety. It is possible to interpret an additional impact on social disability (IHQL) or "usual activities" (EQ-5D) if the coverage of these domains is taken to include sexual functioning. This is not the perspective of this report, although estimates re-calculated to include these additional dimensions have little impact on cost-utility estimates and do not alter the decision band of the result.

As erectile dysfunction is commonly associated with organic disease, men receiving sildenafil treatment may well experience health problems which, irrespective of the impact of ED, cause them to be in a state of less than "full health". The effect of sildenafil treatment on clinical outcomes and health-related quality of life may also vary according to co-morbidity. Accounting for the likely variation in both initial health states and level of improvement would entail estimation far beyond the sophistication of current epidemiological and quality of life data, and as such the presentation of disease-based results is beyond the scope of this report, although estimates of the change in quality of life associated with successful treatment do account for co-morbidity.

The IHQL measure is three dimensional with a range of values over five levels for emotional distress (E), physical disability (D) and pain (P). Of these, ED must be seen as affecting emotional distress. From the IHQL table, a person with no pain, no physical or social disability and slight emotional distress is seen as having a quality of life rating of 0.970; with moderate emotional distress this falls to 0.894. If sildenafil treatment relieves emotional distress, the associated change in health state value will be 0.03 or 0.106, according to initial severity of distress; these changes are unaltered by levels of physical disability and pain. If the average man presenting for treatment is equally likely to suffer slight as moderate emotional distress, the expected change in health state value from successful treatment will be 0.068 [i.e. (0.5*0.03)+(0.5*0.106)].

The EQ-5D classification uses five dimensions with three levels to define 243 possible health states, for which a tariff of health state values has been calculated from a representative sample of the UK population. A person with no problems in mobility, self-care, usual activities or pain but who is moderately anxious or depressed has a health state value of 0.848. If sildenafil treatment relieves this anxiety or depression, the associated change in health state value will be 0.152. However, if problems exist on other dimensions, the treatment-related change in health state value will be 0.071, and the analysis uses this latter, lower, estimate.

For interventions such as sildenafil, which produce relatively small improvements in health-related quality of life, generic quality of life instruments such as the EQ-5D may be insensitive to the changes experienced in patient quality of life. Whilst this is likely in any generic scale aimed by definition to cover the entire range of health care interventions available, it is perhaps a problem suffered more by the EQ-5D (with its 3 levels for each of its 5 attributes) than the IHQL (with 5 levels for its 3 attributes). Against this, we should recognise the sophistication of the EQ-5D in terms of its level of development, validation and use in comparison to the IHQL, and in particular the derivation of a tariff of EQ-5D health state values from a representative sample of the UK general population, as opposed to the expert panel of the IHQL.

Estimating the expected change in quality of life and cost

The analysis compares sildenafil treatment to the "do nothing" alternative, rather than to treatment with alprostadil (either by injections or MUSE). This decision is based on three key factors:

- Patient group: all current predictions of the patient population for sildenafil extend far beyond those currently receiving alprostadil treatment, so whilst for some the relevant comparison will be between sildenafil and alprostadil therapy, for the vast majority the appropriate comparator is no treatment.
- Effectiveness: all available evidence suggests that sildenafil is at least as effective as alprostadil treatment in the major patient groups under study in terms of clinical outcome measures. If this is the case, quality of life effects of sildenafil should be greater than those associated with alprostadil as sildenafil does not require uncomfortable insertion or injection, has fewer side-effects and, if

effective, produces an erection only when sexually aroused rather than automatically, whether desired or not, with alprostadil.
- Cost: the price per tablet of sildenafil is 50-60% that of the price per equivalent dose of alprostadil.

If the above assumptions of cost, effectiveness and quality of life hold, sildenafil treatment will dominate alprostadil treatment in a cost-utility analysis (i.e. less expensive and at least as or more effective).

The analysis makes a number of simplifying assumptions; where these are due to the lack of available evidence on quality of life, assumptions are made such that any bias introduced is against sildenafil treatment and will thus strengthen a result in favour of treatment.

The effectiveness of sildenafil treatment varies from 50% to 80%, according to outcome measure used (see section 5 above). Questions 3 and 4 of the IIEF demonstrate statistically significant improvements in mean scores with sildenafil treatment relative to placebo, however these outcome measures are difficult to interpret in cost-utility analysis. Responses to the general efficacy question show 65-82% of men treated with sildenafil reported improved erections, compared to 18-26% treated with placebo. Currently available event log data show that up to 60% of attempts at intercourse were successful in men treated with sildenafil, and up to 25% of attempts in men receiving placebo; these should be adjusted for baseline success rates when such data become available. The analysis uses the lower estimate of 50%; to the extent that this underestimates true effectiveness, results here will overestimate cost per additional QALY gained.

On balance, the quality of life research concerning erectile dysfunction suggests that such an improvement will be associated with a significant improvement in satisfaction with sexual and overall relationships, self-esteem and overall mental health; such improvements are likely to be greater for those with reduced levels of these quality of life parameters at baseline. The analysis restricts consideration of benefits to the man receiving treatment; to the extent that sildenafil produces benefits to partner(s) and wider family members, results here will overestimate cost per additional QALY gained. Successful sildenafil treatment is associated with a change in health related quality of life using the IHQL or EQ-5D descriptive instruments and associated health state values of 0.068 or 0.071 respectively, as described above.

The time perspective taken is one year; this avoids the need for discounting over time and provides a realistic basis for decision-making. All patients who respond to sildenafil treatment are assumed to maintain treatment for one year, whereas non-responders are assumed to cease treatment after 12 weeks. Improvement in quality of life related to sildenafil treatment is assumed to persist for the full year. Whilst there will be a number of men who respond to treatment yet discontinue due to lack of interest, side-effects or "cure", excluding these groups simplifies the analysis and any bias will be against sildenafil treatment, i.e. overestimating cost per additional QALY gained.

The analysis is performed from the perspective of the NHS. A wider societal perspective would include patient costs of attending GP for prescription, any prescription charge and costs and benefits to the partners and family of sildenafil patients. Whilst there are a range of alternative delivery mechanisms for sildenafil treatment, this analysis assumes GP prescribing in primary care due to the lack of perceived side-effect problems and lack of need for specialist diagnosis and monitoring. Current prices for sildenafil are £4.15 for 25mg, £4.84 for 50mg and £5.87 for 100mg. Studies of sexual functioning from both the US and UK provide summary information on median frequencies of sexual activity.[21; 155-157] Median frequencies in the sexually active population fall from over twice a week in men under 30 to less than once a week in men over 50, who form over 85% of the predicted ED population. The analysis assumes that sildenafil is prescribed at a rate of 1 per week, and at a cost of £4.84 per tablet. Sensitivity of results to these assumptions are explored in the next section. Results are presented in Table 15 below.

Table 15 - Cost-utility analysis

Effectiveness of treatment = 50%	**EQ-5D model**	**IHQL model**
Cost:		
Successfully treated men:		
4 GP consultations @ £15	£60	£60
52 weeks sildenafil treatment @ £4.84 and 1/week	£251.68	£251.68
Annual cost for successfully treated	£311.68	£311.68
Non-responders:		
2 GP consultations @ £15	£30	£30
12 weeks sildenafil treatment @ £4.84 and 1/week	£58.08	£58.08
Annual cost for non-responders	£88.08	£88.08
Expected treatment cost	£243.92	£243.92
QALY gain:		
Successfully treated men:		
EQ-5D QoL gain 0.071, IHQL QoL gain 0.068	0.071	0.068
Non-responders:		
EQ-5D & IHQL QoL gain 0.000	0.000	0.000
Expected QALY gain over 1 year	0.0355	0.034
Cost-utility of sildenafil treatment over no treatment	£6871 per additional QALY gained	£7174 per additional QALY gained

Sensitivity analysis

There is currently a substantial degree of uncertainty over many aspects of male erectile dysfunction, in particular:

- prevalence of complete male erectile dysfunction in the UK population
- proportion of ED sufferers who would be interested in drug therapy to potentially improve their sexual functioning
- proportion of GPs who would be willing to prescribe sildenafil to presenting patients
- proportion of ED sufferers who would respond to placebo
- proportion of patients receiving sildenafil who will halt treatment
- proportion of patients receiving sildenafil who will respond positively
- expression of male erectile dysfunction on a generic health-related quality of life scale
- prescribing rate of sildenafil (tablets per week)
- price of sildenafil per tablet

Whilst this list may depress some readers for the level of uncertainty that remains after 21 randomised clinical trials, it provides much scope for sensitivity analysis.

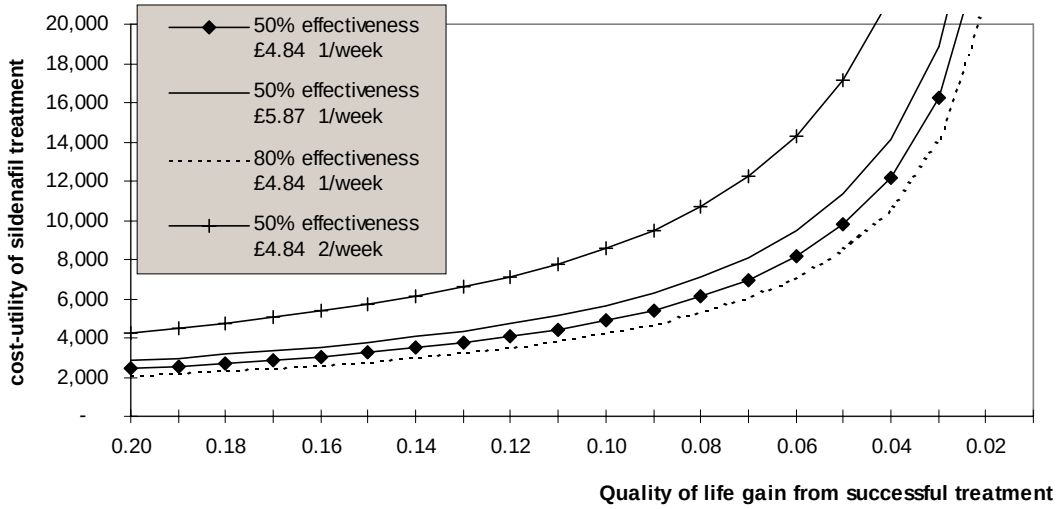
Variation in the first five areas listed above (those in the shaded area) will affect estimates of the total impact (including total cost to the NHS) for a given population, but not cost-utility estimates.

The sensitivity analysis, shown in Table 16 below, allows for variation in the main assumptions made in the above analysis (i.e. variation in treatment effectiveness, price, prescribing rate, and change in health-related quality of life associated with successful treatment). It shows one-way threshold sensitivity analysis for quality of life change from successful treatment, effectiveness of sildenafil treatment and treatment costs, i.e. the values shown indicate the levels of these variables needed to push the cost-utility result into a lower or higher decision band (see page 49). The graph below illustrates sensitivity of results to changes in QoL gain from successful treatment and to the use of higher effectiveness (80%), price (£5.87) or dosing frequency (2 per week) assumptions.

Table 16 - One-way threshold sensitivity analysis

	EQ-5D model	**IHQL model**
Point estimate result of incremental cost-utility ratio of sildenafil treatment over no treatment	£6,871 per additional QALY gained	£7,174 per additional QALY gained
Variable values needed to attain a result below £3,000 per additional QALY gained:		
Expected utility gain:	>0.082	>0.082
attained with effectiveness:	n/a (over £3000 at	100% effectiveness)
or QoL gain from successful treatment:	>0.162	>0.162
Or expected annual cost per patient:	<£160.50	<£102
attained with tablet price:	<£1.22	<£1.10
or prescribing rate:	<0.3 per week	<0.3 per week
Variable values needed to attain a result above £10,000 per additional QALY gained:		
Expected utility gain:	<0.025	<0.025
attained with effectiveness:	<23%	<25%
or QoL gain from successful treatment:	<0.049	<0.049
Or expected annual cost per patient:	>£355	>£340
attained with tablet price:	>£7.75	>£7.37
or prescribing rate:	>1.6 per week	>1.5 per week
Variable values needed to attain a result above £20,000 per additional QALY gained:		
Expected utility gain:	<0.013	<0.013
attained with effectiveness:	<8%	<9%
or QoL gain from successful treatment:	<0.025	<0.025
Or expected annual cost per patient:	>£710	>£680
attained with tablet price:	>£17.10	>£16.32
or prescribing rate:	>3.5 per week	>3.3 per week

Sensitivity of cost-utility result to key assumptions



The sensitivity analysis illustrated above shows the sensitivity of cost-utility results to key assumptions used, and in particular to the assumed degree of improvement in health-related quality of life associated with successful sildenafil treatment. As discussed above, the current evidence on quality of life impact of erectile dysfunction prevents a more precise estimate. However, within a range of 0.05 to 0.15 for QALY gain from successful treatment (i.e. the range provided by the decision analysis studies in section 0, above), the cost-utility varies from around £3,000 to around £20,000 per additional QALY gained; whilst this range maybe too broad to be useful policy information, it fits into a current DEC decision band (see Appendix 1 - Basis for recommendations about the use of interventions, treatments or services, page 54) as "strongly supported".

9 IMPLICATIONS FOR THE NHS

The cost implications for the NHS are hard to predict with precision because of the intrinsic uncertainty surrounding the assumptions about

- the number of men who will present for treatment
- the frequency of use of sildenafil
- possible national policy restrictions on its use

We have produced a model of the possible impact on the NHS drug budget if sildenafil were available for prescription in primary care and used once per week (in line with best evidence about the modal frequency of intercourse by age groups).

The rate of presentation has the most impact on the estimated cost to the NHS. Therefore costs are presented for a range of presentation rates, the model uses different presentation rates by age and the average varies from 38% to 65% of adult males with ED. The model uses current drug prices. It assumes that 70% of men presenting for treatment will be given sildenafil (others being given other treatments, having their current medication modified or being unsuitable for treatment). It also assumes that 40% of people prescribed sildenafil drop out. This estimate is based on anticipated levels of lack of response and the number of people who will cease to require it for social, psychological or medical reasons - this is based on the information from the sildenafil trials and knowledge about drop out rates for MUSE and ICIs.

Total population size	**Presentation rate**	**Annual drug cost** (based on 9.5% prevalence in male population)
100,000	38%	£150,000
100,000	65%	£250,000
500,000	38%	£750,000
500,000	65%	£1,250,000

10 TABLES

Table 17 - Telephone survey of erectile dysfunction and impotence clinics in the W. Midlands - July and August 1998

Impotence Clinic	Frequency	No. of new patients/clinic	Waiting list for clinic	Usual treatment	Comments	Trust	Specialist
Consultant led	1 per week	3	None	MUSE	Alternates location between Stafford DGH and Cannock Chase Hospital	Mid. Staffordshire General Hospital	Mr Murphy (consultant)
Nurse led	1 per week (Thursday)	10-11	8 weeks	MUSE Caverject (-not many prostheses)	The number of patients in each clinic have doubled in the past 12 months	Sandwell	Helen Rock, Sandwell Malcolm Jones (consultant)
GP led	1 per week (Tuesday) (with 2 consultants)	10 new 15-20 routine/f.u.	New appointments: 3 months Follow-ups: 2-3 months	MUSE Invicorp Caverject		Good Hope	Geoff Hatchett (sec.) Good Hope (with Dr Millidge)
Nurse led	3 per week	4	3 months	Assessment → -Psychosexual councillor or - if organic: Yohimbine, Alprostadil (injection) MUSE, Vacuum Combination of above	All patients are asking about Viagra	City Hospital	Margaret Howells City Hospital Peter Ryan (consultant) City Hospital
Consultant led	1 per fortnight	12	3 months	Usual medical treatments plus ~10 surgical implants p.a.		Good Hope	Michael Foster (consultant) Good Hope Hospital
Nurse led	2 per week + 1 per fortnight	10-12	1 year	MUSE Alprostadil		University Hospital Birmingham	Judith Turner Q.E., Birmingham
Nurse led	1 per week (1 week in Shrewsbury, 1 week in Telford)	2	At least 12 months	MUSE Caverject Alprostadil	Waiting list initiative has provided extra funding for extra clinics	Royal Shrewsbury Hospitals	Mr Beacock (consultant) Shrewsbury
Consultant led (Andrology)	1 per month	13	?	Vacuum Caverject MUSE		Royal Wolverhampton Hospitals	Mr Waymont (consultant) Wolverhampton
Consultant led	2 per month	9	1 year	Vacuum Caverject MUSE	Demand for clinic has doubled in the past year.	Royal Wolverhampton Hospitals	Mr Ingles Wolverhampton
Consultant led	1 per fortnight	8	3 months	Injection MUSE Vacuum	There has been an increase in number of enquiries and private patients since Viagra has been in the media	Alexandra Healthcare & Worcestershire Community Healthcare	Mr Lancashire Redditch & Bromsgrove
Consultant led	1 per month	6-8	6/7 months	MUSE	Putting on extra clinics to clear the backlog.	Birmingham Heartlands and Solihull	Mr Jaganathan Solihull/Heartlands
Consultant led	1 per week	4	8 weeks	Vacuum Caverject MUSE (not in stock yet)		Dudley Group of Hospitals	Mr Rowse Russells Hall Dudley
?	?	?	?	?	Unable to contact clinic for further details	Walsgrave Hospital, Coventry	Dr Ashraf Fahmy
Consultant led - new clinic	1 per week	3	2 months	?		Walsall Hospitals	Mr Jasin Manor Hospital, Walsall

Table 18 - Studies of prevalence of erectile dysfunction in male patients with diabetes

Study	Year	Term used and definition	Study size	Respondents	Prevalence of ED	Comments
Klein *et al*[33] (US)	1990-1992	**Impotence/Erectile dysfunction – "the inability to achieve a normal erection"**	359	21-76 year old insulin dependent diabetic men who were <30years old at diagnosis with 10 or more years of IDDM.	**20%** Increased with increasing age 1.1% : 21-30yrs 47.1%: 43yrs + Increased with duration of diabetes	Population based cohort study. Self reported.
McCulloch *et al*[31] (UK)	1980	**Erectile Impotence – "partial or complete failure to obtain an erection for at least six months"**	541	Diabetic males aged 20-59 years attending a diabetic outpatient clinic	**35%** 5.7% aged 20-24 14.3% aged 25-29 15.9% aged 30-34 30.2% aged 35-39 28.8% aged 40-44 36.3% aged 45-49 49.5% aged 50-54 52.4% aged 55-59	Interviewed
Feldman *et al*[13] (US)	1987-1989	**Impotence – "persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance"**	88	Males aged 40-70 year with diabetes that were being treated and taking part in a larger survey	**28%** (age –adjusted probability)	Self-administered sexual activity questionnaire
Nathan *et al*[34] (US)	1986	**Impotence – not defined**	125	NIDDM men aged 55-74 (Mean = 64.3 ±5.4). Outpatients of Massachusetts General Hospital	**56%: 55-64 yrs** **65%: 65-74 yrs**	
Lester et al[158] (UK)	1980	**Impotence – not defined**	83	Diabetic patients aged 15-60 attending a diabetic clinic	**23%** **25%: 21-30 yrs** **11%: 31-40 yrs** **12.5%: 41-50 yrs** **38%: 51-60yrs**	Self-reported

Table 19 - Controlled trials with alprostadil[g]

Ref.	Design	Number patients	Treatment arms	Duration	% patients withdrawn	Erection sufficient for intercourse	NNT	Penile Pain	Prolonged erection
Intracavernosal Alprostadil - Controlled trials (*reporting erectile response*) in the treatment of male erectile dysfunction (n>50**)**									
159	SB CO	205	A 5mcg Pap 18mg	1 dose	37	73% 44%		8.5% 4.7%	0% 0%
160	DB CO	52	A 20mcg Pap 30-60mg	1 dose of each drug	0	81%* 63%*		11.5% 25%	0% 0%
161	DB CO R	54	A 20mcg Pap 60mg	1 dose of each drug	7	46% 14%		45% 44%	0% 0%
162	R CO	38 49	A 10mcg vs. Pap 7.5mg +A 5mcg Pap 7.5mg +A 5mcg vs. Pap 7.5mg + Phent 0.25mg	1 dose of each drug or 1 dose of each drug	0	60.5% 73.6% 77.5% 57%		NR	NR
163	DB CO R PC	60	Placebo A 30mcg Pap 30mg + Phent 0.5mg	1 dose of each solution	0	0% 50% 56%	 2.0 1.8	0% 35% 15%	0% 15% 18%
56	DB PC R	296	59 Placebo 57 A 2.5 mcg 60 A 5mcg 62 A 10mcg 58 A 20mcg	1 dose	0	0 17% 28% 43% 51%	 5.9 3.6 2.3 2.0	0 } 23%	0 } 1.3%
	O	683	A 0.2 – 80mcg	6 months	31	87%		50%	1%
Transurethral alprostadil (MUSE) – Placebo controlled trials									
64	MC DB R PC	68	Placebo MUSE 125mcg MUSE 250mcg MUSE 500mcg MUSE 1000mcg	1 dose of each strength	Not specified	5% 20% 30% 27% 32%	 6.7 4 4.5 3.7	0% 9% 18%	 11% 5.6%
62	MC DB R PC *Pre-selected patients*	996	485 Placebo *Patients selected as* 511 MUSE *responsive to alprostadil* 743 Placebo ***Adjusted** for all patients* 769 MUSE *with ED*	3 months	13	18% 62% 12% 40%	 (2.3) 3.6	3% 33%	3.5
Comparative trial transurethral and intracavernosal alprostadil									
164	O CO	103	MUSE 250 – 1000mcg A 5-20mcg	1 administration of each dose	0	43% 70%		31% 11%	

- just reported as a positive response

Key

O	Open label	SB	Single blind	CO	Crossover	A	Alprostadil IC	Phent	Phentolamine IC
R	Randomised	DB	Double blind	PC	Placebo controlled	Pap	Papaverine IC	MC	Multicentre

[g] Source: Adapted from the Sildenafil report by MTRAC[167]

Table 20 - Phase II Trials - Using Clinical Outcomes

Study Number	Design	Cause of ED	Patient Characteristics	No. of patients	Interventions	Duration	Efficacy Outcomes Measured	References
351	Pilot study Fixed dose Crossover	No established organic cause	Mean age 50 years Mean duration of ED 3.4 yrs	12	Placebo Sildenafil 10mg Sildenafil 25mg Sildenafil 50mg Placebo Sildenafil 25mg	1 dose 1 dose 1 dose 1 dose *separated by a 3 day washout* 7 days x 2 separated by a 1 week washout	Rigiscan Patients diary GEQ	FDA-NDA[91] Boolell *et al* 1996 (P) [70]
357	Fixed dose Crossover *No washout specified*	Diabetes	Mean age 50 years Mean duration of ED 3 years Diabetes>5 years	21	Placebo Sildenafil 25mg Sildenafil 50mg Placebo Sildenafil 25mg Sildenafil 50mg	1 dose 1 dose 1 dose 10 days	RigiScan Event log Questionnaire GEQ	Boolell *et al* 1996[99] (Abs) FDA-NDA[100]
358	Fixed dose Crossover Parallel group	SCI (cord level T6-L4/5)	Mean age 33 years Mean duration of ED 6 years	27	Placebo Sildenafil 50mg 14 Placebo 12 Sildenafil 50mg	1 dose 1 dose *separated by at least 3 day washout* 4 weeks	Rigiscan Questionnaire GEQ Event log	FDA-NDA[101] Dinsmore WW *et al* 1997[102] (Abs) Derry F et a 1997l[103] (Abs)
101	Fixed dose Parallel group *2-4 week treatment free run in*	Broad aetiology	Mean age 57.6 years Mean duration of ED 4.6	416	82 Sildenafil 25mg 83 Sildenafil 50mg 82 Sildenafil 100mg	24 weeks	IIEF - Q1 - 1^0 endpoint GEQ Partner Questionnaire Event log	FDA-NDA[82] Leu *et al* 1997[83] (Abs)
353	Fixed dose Parallel group *2 week treatment free run in*	No established organic cause	Mean age 53 years Mean duration of ED 4.5 years	351	95 Placebo 90 Sildenafil 10mg 85 Sildenafil 25mg 81 Sildenafil 50mg	4 weeks	IIEF Event log GEQ	FDA-NDA[92] Dinsmore WW *et al* 1996[93] (Abs)
355	Variable dose Crossover *3 week treatment free run in*	No established organic cause	Mean age 53 years Mean duration of ED 3 years	44	43 Placebo 44 Sildenafil 25-75mg *no washout period*	4 weeks x2 no washout	GEQ Event log	FDA-NDA[94] Eardley I *et al* 1996[95] (Abs)
356	Variable dose Parallel group	Broad aetiology	Mean age 54 years Mean duration of ED 4.9 yrs	205	106Placebo 99 Fixed dose of sildenafil 10,25,50 or 100mg *-(determined in open study)*	8 weeks	GEQ Questionnaire Event log	FDA-NDA[96] Bailey *et al* 1997[97](Abs) Virag R *et al* 1996[98](Abs)
359	Variable dose Parallel group *2 - 4 treatment free run in period*	Broad aetiology	Mean age 56 years Mean duration of ED 4.5 yrs	111	54 Placebo 57Sildenafil 25-100mg	12 weeks	GEQ - 1^0 endpoint IIEF Event log	FDA-NDA[104] Abel P *et al* 1997[105] (Abs)
361	Fixed dose Parallel group *2 week treatment free run in,*	Organic aetiology (excluding SCI)	Mean age 57 years Mean duration of ED 5.2 yrs	254	59 Placebo 62 Sildenafil 50mg 66 Sildenafil 100mg 67 Sildenafil 200mg	12 week	IIEF - Q1 GEQ Event log	FDA-NDA[109]

Table 21 - Phase III Trials[h]

Study Number	Design	Cause of ED	Patient Characteristics	Number of patients	Interventions	Duration	Outcomes	References
102	Fixed Dose Parallel group *4 week treatment free run in*	Broad aetiology	Mean age 57.6 years Mean duration of ED 3.2yrs	532	216 placebo, 102 sildenafil 25mg, 107 sildenafil 50mg 107 sildenafil 100mg	24 weeks	IIEF(Q3 &Q 4 1^0 endpoint) GEQ Event log	FDA-NDA[84] Goldstein *et al* 1998[69] (P)
103	Variable dose Parallel group *4 week treatment free run in*	Broad aetiology	Mean age 59.5 years Mean duration of ED 4.8 yrs	329	166 placebo 163 sildenafil 25-100mg	12 weeks	IIEF (Q3 &Q 4 1^0 endpoint) GEQ Event log	FDA-NDA[85] Goldstein *et al* 1998[69] (P)
104	Variable dose Parallel group *4 week treatment free run in*	Diabetes	Mean age 57 years Mean duration of ED 5.6 yrs Mean duration of diabetes 12.1 yrs 18.7% type 1 81.3 % type 2 diabetes	268	132Placebo 136 Sildenafil 25-100mg	12 weeks	IIEF (Q3 &Q4) GEQ Partner questionnaire QoL questionnaire Event log	FDA-NDA[86] Rendell *et al* 1998[87] (Abs)
364	Fixed dose Parallel group *4 week treatment free run in*	Broad aetiology	Mean age 55.8 years Duration of ED 4.8 years	514	127 Placebo 128 Sildenafil 25mg 132 Sildenafil 50mg 127 Sildenafil 100mg	12 weeks	IIEF (Q3 & Q4) GEQ Event log QoL questionnaire	FDA-NDA[112]
363	Variable dose Parallel group *4 week treatment free run in,*	Broad aetiology	Mean age 54.5 years Mean duration 4.8 years	315	156 Placebo 159 Sildenafil 25-100mg	26 weeks	IIEF (Q3 & Q4 - at wk 12) GEQ partner questionnaire Event log QoL questionnaire	FDA-NDA[110] Cuzin B *et al* 1997[111] (Abs)
367	Variable dose Crossover *4 week treatment free run in,*	SCI	Mean age 38 years Mean duration of ED 11 years	178	Placebo Sildenafil 50mg	6 weeks x 2 *separated by a 2 week washout*	GEQ (1^0 endpoint) IIEF (Q3 & Q4) Event log Partner Questionnaire QoL questionnaire	FDA-NDA[113] Holmgren E *et al* 1998[114] (Abs)
106	Fixed dose Parallel group *4 week treatment free run in*	Broad aetiology	Mean age 58 years Mean duration of ED 5.4 yrs	497	122 placebo 127 Sildenafil 50mg 124 Sildenafil 100mg 124 Sildenafil 200mg	12 weeks	IIEF (Q3 &Q 4 1^0 endpoint) GEQ Event log Partner questionnaire QoL questionnaire	FDA-NDA[89]

P - published Abs - Abstract

[h] all are randomised, double-blind, placebo-controlled trials in men with ED

Appendix 1 - Basis for recommendations about the use of interventions, treatments or services

Code for categorising the quality of the evidence:

I	At least one properly designed, randomised controlled trial
II	Well-designed controlled trials or well-designed cohort or case-control analytic studies, preferably from more than one centre or research group Or multiple time-series or dramatic results in uncontrolled experiments
III	Opinions of respected authorities based on clinical evidence, descriptive studies or reports of expert committees
IV	Evidence inadequate owing to problems of methodology (e.g. sample size, length or comprehensiveness of follow-up) or conflicts of evidence

West Midlands Development and Evaluation Service (DEC)

Evidence	<£3000 per QALY	£3000 - £20,000 / QALY	>£20,000 per QALY	Negative QALYs
I	Strongly Supported	Strongly Supported	Borderline	Not Recommended
II	Strongly Supported	Supported	Borderline	Not Recommended
III	Supported	Borderline	Borderline	Not Recommended
IV	Not Proven	Not Proven	Not Proven	Not Proven

Appendix 2 - Drugs associated with erectile dysfunction

Antihypertensives	Drugs with endocrine effects	CNS agents
β-blockers, e.g. Propranolol	Spironolactone	Phenothiazines
Thiazides, e.g. Bendrofluazide	Cimetidine	Haloperidol
Spironolactone	Metoclopramide	Tricyclic antidepressants
Methyldopa	Bezafibrate	SSRIs
Reserpine	Alcohol (ethanol)	Butyrophenone
	Corticosteroids	Benzodiazepines
	Gonadotrophic releasing hormone agonists	MAOIs
	Marijuana	Lithium

Adapted from: Chaudhuri J. & Wiles P.[165]

Appendix 3 - Package Insert[2]

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA▼ 25 mg film-coated tablets.
VIAGRA 50 mg film-coated tablets.
VIAGRA 100 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg , 50 mg or 100 mg sildenafil as citrate.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The 25 mg tablets are blue film-coated, rounded diamond-shaped tablets, marked "PFIZER" on one side and "VGR 25" on the other.

The 50 mg tablets are blue film-coated, rounded diamond-shaped tablets, marked "PFIZER" on one side and "VGR 50" on the other.

The 100 mg tablets are blue film-coated, rounded diamond-shaped tablets, marked "PFIZER" on one side and "VGR 100" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for VIAGRA to be effective, sexual stimulation is required.

VIAGRA is not indicated for use by women.

4.2 Posology and method of administration

For oral use.

Use in adults

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If VIAGRA is taken with food, the onset of activity may be delayed compared to the fasted state (see Section 5.2 Pharmacokinetic properties - Absorption).

Use in the elderly

Since sildenafil clearance is reduced in elderly patients (see Section 5.2 Pharmacokinetic properties), a first dose of 25 mg should be used. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired renal function

The dosing recommendations described in "Use in adults" apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min).
Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired hepatic function

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in children

VIAGRA is not indicated for individuals below 18 years of age.

4.3 Contra-indications

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see Section 5.1 Pharmacodynamic properties), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its coadministration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contra-indicated.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contra-indicated until further information is available: severe hepatic impairment, hypotension (blood pressure<90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see Section 5.1 Pharmacodynamic properties) and as such potentiates the hypotensive effect of nitrates (see Section 4.3 Contra-indications).

Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil

***In vitro* studies:**
Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

***In vivo* studies:**
Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with sildenafil (50 mg) to healthy volunteers. When a single 100 mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg b.i.d. for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC).

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

Effects of sildenafil on other medicinal products

***In vitro* studies:**

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50}>150 microM). Given sildenafil peak plasma concentrations of approximately 1 microM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

***In vivo* studies:**
No significant interactions were shown when sildenafil (50 mg) was coadministered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was coadministered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers (see Section 5.1 Pharmacodynamic properties).

Consistent with its known effects on the nitric oxide/cGMP pathway (see Section 5.1 Pharmacodynamic properties), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its coadministration with nitric oxide donors or nitrates in any form is therefore contra-indicated (see Section 4.3 Contra-indications).

4.6 Use during pregnancy and lactation

VIAGRA is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

4.7 Effects on ability to drive and use machines

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to VIAGRA, before driving or operating machinery.

4.8 Undesirable effects

The following adverse reactions (with incidence>1%) were reported in patients treated with the recommended dosing regimen in clinical trials:

Cardiovascular: Headache (12.8%), Flushing (10.4%), Dizziness (1.2%)
Digestive: Dyspepsia (4.6%)
Respiratory: Nasal congestion (1.1%)
Special senses: Altered vision (1.9%; mild and transient, predominantly colour tinge to vision, but also increased perception of light or blurred vision)

In fixed dose studies, dyspepsia (12%), and altered vision (11%) were more common at 100 mg than at lower doses.

In addition, there were reports of muscle aches when sildenafil was administered more frequently than the recommended dosing regimen**.** In post marketing surveillance priapism has been reported.

Adverse reactions were mild to moderate in nature and the incidence and severity increased with dose.

4.9 Overdose

In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction. ATC Code: G04B E (proposed)

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil has between 80 and 10,000-fold greater selectivity for PDE5 than for other phosphodiesterase isoforms (PDE's 1,2,3 and 4). In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina.

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plesthysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast sensitivity.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Further information on clinical trials

In clinical trials sildenafil was administered to more than 3000 patients aged 19-87. The following patient groups were represented: elderly (21%), patients with hypertension (24%), diabetes mellitus (16%), ischaemic heart disease and other cardiovascular diseases (14%), hyperlipidaemia (14%), spinal cord injury (6%), depression (5%), transurethral resection of the prostate (5%), radical prostatectomy (4%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see Section 4.3 Contra-indications).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.
Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long term studies.

5.2 Pharmacokinetic properties

Absorption

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100 mg).

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Distribution

The mean steady state volume of distribution (V_{ss}) for sildenafil is 105 l, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Metabolism

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half life of approximately 4 h.

Elimination

The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

Pharmacokinetics in special patient groups

Elderly
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and C_{max} of the N-desmethyl metabolite increased

126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance<30 ml/min), sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 79% and 200% respectively.

Hepatic insufficiency
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate.

Film coat: hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Do not store above 30^{o}C. Keep tablets in the original package, protected from moisture.

6.5 Nature and content of container

Aclar/Aluminium foil blisters in cartons of 1, 4, 8 or 12 tablets.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/98/077/001 - Viagra tablets 25 mg; pack size 1 tablet
EU/1/98/077/002 - Viagra tablets 25 mg; pack size 4 tablets
EU/1/98/077/003 - Viagra tablets 25 mg; pack size 8 tablets
EU/1/98/077/004 - Viagra tablets 25 mg; pack size 12 tablets
EU/1/98/077/005 - Viagra tablets 50 mg; pack size 1 tablet
EU/1/98/077/006 - Viagra tablets 50 mg; pack size 4 tablets
EU/1/98/077/007 - Viagra tablets 50 mg; pack size 8 tablets
EU/1/98/077/008 - Viagra tablets 50 mg pack size 12 tablets
EU/1/98/077/009 - Viagra tablets 100 mg; pack size 1 tablet
EU/1/98/077/010 - Viagra tablets 100 mg; pack size 4 tablets
EU/1/98/077/011 - Viagra tablets 100 mg; pack size 8 tablets
EU/1/98/077/012 - Viagra tablets 100 mg; pack size 12 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 SEPTEMBER 1998

10. DATE OF REVISION OF THE TEXT

AUGUST 1998

11. LEGAL CATEGORY

POM

VIAGRA™TABLETS PACKAGE LEAFLET

Please read this leaflet carefully.

- This leaflet contains a summary of important information about your VIAGRA 25mg, 50mg or 100mg film-coated tablets.
- Please read it carefully **before** you start taking this medicine.
- Keep this leaflet. You may want to read it again.
- If you do not understand anything in the leaflet, or you have further questions, please ask your doctor or pharmacist.

This medicine has been prescribed for you personally. You must not give it to anybody else, even if their symptoms are the same as yours.

Name of the medicinal product

VIAGRA 25 mg film-coated tablets.
VIAGRA 50 mg film-coated tablets.
VIAGRA 100 mg film-coated tablets.

What does VIAGRA contain ?

The active substance of VIAGRA is called sildenafil. Each tablet contains 25mg, 50mg or 100mg of sildenafil (as citrate).

VIAGRA also contains the following inactive excipients:
Tablet core: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate.
Film coat: hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132).

VIAGRA film-coated tablets are blue, with a rounded-diamond shape. They are marked "PFIZER" on one side and "VGR 25" , "VGR 50" or "VGR 100" on the other side. The tablets are provided in blister packs containing 1, 4, 8 or 12 tablets.

What is VIAGRA ?

VIAGRA belongs to a group of medicines called phosphodiesterase type 5 inhibitors. It works by helping to relax the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited. VIAGRA will only help you to get an erection if you are sexually stimulated. You should not take VIAGRA if you do not have erectile dysfunction. You should not take VIAGRA if you are a woman.

Marketing Authorisation Holder and Manufacturing Authorisation Holder

The marketing authorisation holder is Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom.

VIAGRA is made by Pfizer S.A., Zone Industrielle de Pocé-sur-Cisse, 37401 Amboise Cedex, France.

Why take or use VIAGRA ?

VIAGRA is a treatment for men with erectile dysfunction, sometimes known as impotence. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

When should you NOT take VIAGRA ?

Do NOT take VIAGRA if :

- you are taking medicines containing nitrates, or nitric oxide donors such as amyl nitrite ("poppers"). These medicines are often given for relief of angina pectoris (or "chest pain"). VIAGRA can cause a serious increase in the effects of these medicines. Tell your doctor if you are taking any of these medicines. If you are not certain, ask your doctor or pharmacist.

- you have ever had an allergic reaction to VIAGRA or any other ingredient listed under "**What does VIAGRA contain ?"**. An allergic reaction can be a rash, itching, a swollen face, swollen lips or shortness of breath. If this has ever happened to you, tell your doctor.

- you have a severe heart or liver problem.

- you have recently had a stroke or a heart attack, or if you have low blood pressure.

- you have certain rare inherited eye diseases (such as retinitis pigmentosa).

When should VIAGRA be used with caution ?

You should tell your doctor:

- if you have sickle cell anaemia (an abnormality of red blood cells), leukaemia (cancer of blood cells), multiple myeloma (cancer of bone marrow) or any disease or deformity of your penis. These conditions may require special care when taking medicines for erectile dysfunction.

- if you currently have a stomach ulcer, or a bleeding disorder (such as haemophilia).

You should not use VIAGRA with any other treatment for erectile dysfunction.

Are there special considerations for children ?

VIAGRA should not be given to children under the age of 18.

Are there special considerations for elderly patients over 65 years of age ?

If you are elderly, your first dose of VIAGRA should be adjusted.

Are there special considerations for patients with kidney or liver problems ?

You should tell your doctor if you have kidney or liver problems. Your doctor may decide that your dose should be different.

Can you drive while taking VIAGRA ?

VIAGRA can cause dizziness and effects on vision. You should be aware of how you react to VIAGRA before you drive or operate machinery.

Can VIAGRA be taken with other medicines ?

You should tell your doctor about all the medicines that you are taking. VIAGRA tablets may interfere with some medicines, especially those used to treat chest pain. In the event of a medical emergency, you should tell anyone treating your condition that you have taken VIAGRA. Do not take VIAGRA with other medicines unless your doctor tells you that you can.

VIAGRA may cause a serious increase in the effects of medicines called nitrates, and nitric oxide donors such as amyl nitrite ("poppers"). These are often used for the relief of angina pectoris (or "chest pain"). You should NOT take VIAGRA if you are taking these medicines.

How should you take VIAGRA Tablets ?

Your doctor will decide which dose of VIAGRA is most suitable for you. You must not take more tablets than your doctor has told you to.

You should take VIAGRA about one hour before sexual activity. Swallow the tablet whole with some water.

VIAGRA will only help you to get an erection if you are sexually stimulated. It will not give you an erection if you are not sexually stimulated. The amount of time VIAGRA takes to work varies from person to person, but it normally takes between half an hour and one hour. You may find that VIAGRA takes longer to work if you take it with a heavy meal.

Drinking alcohol can temporarily impair the ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink large amounts of alcohol before taking VIAGRA.

If VIAGRA does not help you to get an erection, or if your erection does not last long enough for you to complete sexual intercourse you should tell your doctor.

You should not use VIAGRA more than once a day.

What if you take too many tablets ?

A dose above 100 mg does not increase the efficacy. However, it will result in an increase in undesirable effects and their severity.

You should not take more tablets than your doctor tells you to.

If you take more tablets than you have been told to take contact your doctor.

Does VIAGRA cause any undesirable effects ?

VIAGRA may cause some undesirable effects. These effects are normally mild to moderate in nature.

The most common undesirable effects are headache and facial flushing. Less commonly reported undesirable effects are indigestion, dizziness, stuffy nose and effects on vision (including colour tinge to vision, increased brightness of light or blurred vision).

Muscle aches can occur if VIAGRA is taken more frequently than once a day.

Rarely, prolonged and sometimes painful erections have been reported after taking VIAGRA. If you have such an erection which lasts continuously for more than 4 hours, you should contact a doctor immediately.

If you have any of these undesirable effects ***and they are troublesome, severe, or do not go away as treatment goes on***, tell your doctor.

If you notice any undesirable effects of VIAGRA that are not mentioned in this leaflet, please tell your doctor or pharmacist.

How should you store your Viagra tablets ?

Do NOT take this medicine after the expiry date shown on the pack.

Do not store above 30^{o}C. Keep tablets in the original package, protected from moisture.

Keep VIAGRA out of the reach of children.

This leaflet was last revised 25 August 1998.

Other Information

If you have any further questions please consult your doctor or pharmacist.

For any other information about VIAGRA, please contact the local representative of the Marketing Authorisation Holder:

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VIAGRA™ ▼ Tablets (sildenafil citrate)
ABBREVIATED PRESCRIBING INFORMATION UK

Please refer to the SmPC before prescribing VIAGRA 25mg, 50mg or 100mg. Presentation: Blue film-coated, rounded diamond-shaped tablets containing sildenafil citrate equivalent to 25mg, 50mg and 100mg sildenafil. Indications: Erectile dysfunction. Sexual stimulation is required for efficacy. Not for use by women. Dosage: Adults; 50mg approximately one hour before sexual activity. Adjust dose based on efficacy and toleration. Maximum dose is 100 mg. One single dose per day is recommended. If taken with food, the onset of activity may be delayed. Elderly: a first dose of 25 mg should be used. Hepatic impairment, severe renal impairment; 25mg initial dose should be considered; adjust dose based on efficacy and toleration. Children under 18 years; Not indicated. Contraindications: Co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form; patients for whom sexual activity is inadvisable (*e.g.* patients with severe cardiovascular disorders); severe hepatic impairment; hypotension; recent stroke or myocardial infarction; known hereditary degenerative retinal disorders; hypersensitivity to sildenafil or to any of the excipients. Pregnancy and lactation.: Not indicated for women. Warnings and precautions: A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes Cardiovascular status, as sexual activity is associated with cardiac risk. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure and as such potentiates the hypotensive effects of nitrates Patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or predisposed to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia). Patients with bleeding disorders or active peptic ulceration. Not recommended in combination with other treatments for erectile dysfunction. Drug Interactions: In combination with inhibitors of CYP3A4 eg ketoconazole, erythromycin, cimetidine, a 25mg starting dose should be considered. Potentiates the hypotensive effects of nitrates (see contra-indications). Small, additional reduction in blood pressure with amlodipine. No potentiation of the increase in bleeding time caused by acetyl salicylic acid (150mg) or the hypotensive effects of alcohol. No data on non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole. Side-effects: Clinical study experience: headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision (colour tinge, increased perception of light or blurred vision). Dyspepsia and altered vision more common at 100mg. Muscle aches when sildenafil administered more frequently than recommended. Post marketing experience: Priapism. Driving and operating machinery. Caution if affected by dizziness or altered vision. Legal category: POM. Basic NHS cost: Packs of 4, 25mg tablets [EU/1/98/077/002] £16.59; Packs of 8, 25mg tablets [EU/1/98/077/003] £33.19; Packs of 4, 50mg tablets [EU/1/98/077/006] £19.34; Packs of 8, 50mg tablets [EU/1/98/077/007] £38.67; Packs of 4, 100mg tablets [EU/1/98/077/010] £23.50; Packs of 8, 100mg tablets [EU/1/98/077/011] £46.99. Marketing Authorisation Holder: Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

Further information on request:

logo

Pfizer Limited, Sandwich, Kent, CT13 9NJ

Last revised: 3 September 1998

Appendix 4 - Letter to Rt. Hon Alan Milburn, MP from the BAUS

Appendix 5 - International Index of Erectile Function – IIEF

This assessment tool was developed by Pfizer, specifically to evaluate the effects of sildenafil treatment in ED

The IIEF is a self-administered questionnaire designed to measure erectile function, and detect treatment-related changes. It takes around 15 minutes to complete and consists of 15 questions across 5 domains of male sexual function:

Domain	Questions	Possible Score	Mean Score Patients ED	Controls
Erectile function	1-5 + 15	1 - 30	10.7 ± 6.5	25.8 ± 7.6
Orgasmic function	9 & 10	0 – 10	5.3 ± 3.2	8.8 ± 2.9
Sexual desire	11 & 12	2 – 10	6.3 ± 1.9	7.0 ± 1.8
Intercourse satisfaction	6 – 8	0 – 15	5.5 ± 3.0	10.6 ± 3.9
Overall satisfaction	13 & 14	2 – 10	4.4 ± 2.3	8.6 ± 1.7

The mean scores for each question for patients with ED and those without have also been calculated.

Question	Mean score ED patients	Mean score non-ED patients
Q1: Erection frequency	2.27	4.38
Q2: Erection firmness	1.72	4.45
Q3: Penetration ability	1.72	4.34
Q4: Maintenance frequency	1.56	4.28
Q5: Maintenance ability	1.44	4.24
Q6: Intercourse frequency	1.95	2.44
Q7: Intercourse satisfaction	1.65	4.27
Q8: Intercourse enjoyment	1.83	3.85
Q9: Ejaculation frequency	2.52	4.38
Q10: Orgasm frequency	2.43	4.38
Q11: Desire frequency	3.28	3.70
Q12: Desire level	2.94	3.30
Q13: Overall satisfaction	1.77	4.22
Q14: Relationship satisfaction	2.52	4.41
Q15: Erection confidence	1.55	4.13

The IIEF validation procedure appears to have established this instrument as being specific for sexual function, but the relationship between responses to the questionnaire and actual performance has not been addressed.

The IIEF has only been evaluated in short-term studies (up to 12 weeks), its applicability in long-term follow-up studies is therefore not known. It also has not been evaluated in patients excluded from trials

with sildenafil, e.g. those with anatomical difficulties such as Peyronies disease. Further studies are required to determine whether this instrument is valid in these circumstances.

Currently the IIEF is being investigated/validated as a diagnostic tool. It is hoped that it will enable physicians to differentiate between mild, moderate and severe disease.

International Index of Erectile Function (IIEF)

These questions ask about the effects your erection problems have had on your sex life over the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

- sexual activity includes intercourse, caressing, foreplay and masturbation
- sexual intercourse is defined as vaginal penetration of the partner (you entered your partner)
- sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
- ejaculate: the ejection of semen from the penis (or the feeling of this)

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?
   Please check one box only

   [ ] No sexual activity

   [ ] Almost never or never
   [ ] A few times (much less than half the time)
   [ ] Sometimes (about half the time)
   [ ] Most times (much more than half the time)
   [ ] Almost always or always

2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?
   Please check one box only

   [ ] No sexual stimulation

   [ ] Almost never or never
   [ ] A few times (much less than half the time)
   [ ] Sometimes (about half the time)
   [ ] Most times (much more than half the time)
   [ ] Almost always or always

The next three questions will ask about the erections you may have had during sexual intercourse

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
   Please check one box only

   [ ] Did not attempt intercourse

   [ ] Almost never or never
   [ ] A few times (much less than half the time)
   [ ] Sometimes (about half the time)
   [ ] Most times (much more than half the time)
   [ ] Almost always or always

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
Please check one box only

[ ] Did not attempt intercourse

[ ] Almost never or never
[ ] A few times (much less than half the time)
[ ] Sometimes (about half the time)
[ ] Most times (much more than half the time)
[ ] Almost always or always

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
Please check one box only

[ ] Did not attempt intercourse

[ ] Extremely difficult
[ ] Very difficult
[ ] Difficult
[ ] Slightly difficult
[ ] Not difficult

6. Over the past 4 weeks how many times have you attempted sexual intercourse?
Please check one box only

[ ] No attempts
[ ] 1-2 attempts
[ ] 3-4 attempts
[ ] 5-6 attempts
[ ] 7-10 attempts
[ ] 11+ attempts

7. Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?
Please check one box only

[ ] Did not attempt intercourse

[ ] Almost never or never
[ ] A few times (much less than half the time)
[ ] Sometimes (about half the time)
[ ] Most times (much more than half the time)
[ ] Almost always or always

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?
Please check one box only

[ ] No intercourse

[ ] Very highly enjoyable
[ ] Highly enjoyable
[ ] Fairly enjoyable
[ ] Not very enjoyable
[ ] No enjoyment

9. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you ejaculate?
Please check one box only

[ ] Did not attempt intercourse

[ ] Almost never or never
[ ] A few times (much less than half the time)
[ ] Sometimes (about half the time)
[ ] Most times (much more than half the time)
[ ] Almost always or always

10. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm (with or without ejaculation)?
Please check one box only

[ ] Did not attempt intercourse

[ ] Almost never or never
[ ] A few times (much less than half the time)
[ ] Sometimes (about half the time)
[ ] Most times (much more than half the time)
[ ] Almost always or always

The next two questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (for example masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.

11. Over the past 4 weeks how often have you felt sexual desire?
Please check one box only

[ ] Almost never or never
[ ] A few times (much less than half the time)
[ ] Sometimes (about half the time)
[ ] Most times (much more than half the time)
[ ] Almost always or always

12. Over the past 4 weeks how would you rate your level of sexual desire?
Please check one box only

[ ] Very high
[ ] High
[ ] Moderate
[ ] Low
[ ] Very low or none at all

13. Over the past 4 weeks how satisfied have you been with your overall sex life?
Please check one box only

[ ] Very satisfied
[ ] Moderately satisfied
[ ] About equally satisfied and dissatisfied
[ ] Moderately dissatisfied
[ ] Very dissatisfied

14. Over the past 4 weeks how satisfied have you been with your sexual relationship with your partner?
Please check one box only

[ ] Very satisfied
[ ] Moderately satisfied
[ ] About equally satisfied and dissatisfied
[ ] Moderately dissatisfied
[ ] Very dissatisfied

15. Over the past 4 weeks how do you rate your confidence that you can get and keep your erection?
Please check one box only

[ ] Very high
[ ] High
[ ] Moderate
[ ] Low
[ ] Very low

Thank you for completing this questionnaire.

Appendix 6 - FDA Postmarketing Surveillance Report

Postmarketing Safety of Sildenafil Citrate (Viagra)

In response to Freedom of Information requests, the FDA is posting a summary of reports of death in sildenafil citrate (Viagra) users. This posting does not suggest a change in FDA's perspective concerning the safety of Viagra. The intent is simply to provide easier access for those who have requested this information.

The limitations of postmarketing, spontaneous adverse drug event data should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: awareness by health professionals and consumers of adverse drug event reporting, seriousness of the reaction, market share of the drug, length of time since marketing, publicity about a drug or an adverse event, litigation, and regulatory actions.
- Because of underreporting and uncertainty concerning the number of persons exposed to a drug, it is not possible to calculate a true incidence rate of a particular event for a specified drug. In addition, comparisons of drug safety cannot be calculated from these data.
- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete. Follow-up information may not be available.
- An accumulation of adverse event reports does not necessarily indicate that the adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s).

The reports summarised below have been reviewed to eliminate duplicates. Numbers of reports from a computerised listing of the Adverse Event Reporting System (AERS) should therefore not be expected to match the numbers below, as those listings also contain duplicate reports and reports that are little more than hearsay.

Summary of Reports of Death in Viagra Users Received from Marketing (late March) through July 1998

From the marketing of sildenafil citrate (Viagra) in late March through July 1998, during which more than 3.6 million outpatient prescriptions were dispensed, the FDA received reports of 123 patients who died after having been prescribed this drug. Twelve deaths concerned foreign patients and 30 concerned patients with unverifiable information (from hearsay, rumor, the media, or unidentifiable reporters). In addition, reporters stated that they did not know if the drug had been used for 12, leaving 69 U.S. patients who died after having taken Viagra. Of these, cause of death was unmentioned or unknown for 21, two patients had strokes, and 46 had cardiovascular events (21 with definite or suspected myocardial infarction, 17 with cardiac arrest, 4 with cardiac symptoms, 3 with coronary artery disease, and one with severe hypotension leading to cardiac arrest).

Of the 69 U.S. patients, 66 with gender specified were men. Age was provided for 55 individuals whose average age was 64 years (median = 64, range = 29-87). Of 31 with dose reported, 26 had taken the 50 mg dose, 3 had taken the 100 mg dose, and 2 were prescribed 50-100 mg. Twelve men self-medicated or were administered nitroglycerin or a nitrate medication that is contraindicated with the use of Viagra.

Time from use of Viagra to death or onset of symptoms leading to death was examined since the drug is taken periodically and since a direct effect of the drug would be limited to a finite period after drug ingestion. Twenty-five (36%) of the 69 patients died or had onset of symptoms leading to death within 4 to 5 hours of drug use (including 18 during or immediately after sexual intercourse). Three died or developed symptoms later the same day of Viagra use; 7, the next day; 4, two days later; and 2, three to four days after Viagra use. The time from drug ingestion to death or onset of symptoms leading to death was not stated or was unknown for 28 men (41%).

Fifty-one (74%) of the 69 patients had one or more risk factors reported for cardiovascular or cerebrovascular disease (hypertension, hypercholesterolaemia, cigarette smoking, diabetes mellitus, obesity, previous cardiac history). Three additional persons without identified heart disease or risk

factors had severe coronary artery disease detected at autopsy. Five were reported to have no previous history of cardiac disease or risk factors.

As with all approved medications, the FDA will continue to monitor the postmarketing safety of Viagra by carefully reviewing reports of death and other serious adverse events and will continue to evaluate the need for regulatory action.

Taken from: http://www.fda.gov/cder/consumerinfo/viagra/viagraupdate721.htm

Appendix 7 – IHQL

Index of Health Related Quality of Life (Rosser et al)

The IHQL provides a broad and sensitive measure of social, psychological and physical functioning, and is designed to be applicable across all diagnostic groups. Using this instrument, it is possible to derive an assessment of health status on a single unidimensional scale,

The IHQL is derived from the original two-dimensional Rosser Index based on the dimensions of disability and distress. In this scale, distress is separated into physical and emotional components, to give three dimensions (disability, physical distress and emotional distress).

3-Dimensional Classification
Disability

D1: No physical disability; perfectly mobile and physically active; able to perform all self-care and role functions.

D2: Slight social disability, e.g. having a slight cold. No limitations with physical ability, self-care or mobility, but some role functions slightly impaired by social disability

D3: Slight physical disability. Able to get round house and community, but unable to perform heavy physical tasks. Role functions slightly limited by physical disability. Able to perform all self-care activities.

D4: Able to get round house and do lighter physical work. Some difficulty in getting community due to weakness or other physical limitations. Can perform all self-care activities. Ability to perform role functions limited.

D5: Difficulty in getting around house, can only go out with assistance. Major physical limitations, e.g. can only do light work. Can perform most self-care activities, but need help getting in and out of the bath. Limited ability to perform role functions.

D6: Confined to a chair, therefore can only get out with assistance. Can only do the lightest of tasks, e.g. switch on the TV. Can feed self, but needs help with all other health care activities. Very limited ability to perform role functions.

D7: Confined to bed. Needs help with all self-care activities. Minimal ability to perform role functions.

D8: Unconscious

Discomfort (Physical)
P1: No pain
P2: Slight pain: (a) occasionally, (b) frequently. (c) almost all the time
P3: Moderate pain: (a) occasionally, (b) frequently. (c) almost all the time
P4: Severe pain: (a) occasionally, (b) frequently. (c) almost all the time
P5: Agonising pain: (a) occasionally, (b) frequently. (c) almost all the time

Distress (Emotional)

E1:	**No distress: very happy and relaxed almost all of the time.**
E2:	**Slight distress: happy and relaxed most of the time, but anxious and depressed some of the time.**
E3:	**Moderate distress: anxious and depressed most of the time, but happy and relaxed some of the time.**
E4:	**Severe distress: very anxious and depressed almost all of the time.**
E5:	**Extremely depressed: actively suicidal.**

Composite state valuations (0-1 scale of values)

		E1	E2	E3	E4	E5
P1	D1	1,000	0.970	0.894	0.791	0.643
	D2	0.990	0.960	0.884	0.781	0.632
	D3	0.971	0.940	0.864	0.762	0.614
	D4	0.946	0.917	0.840	0.738	0.590
	D5	0.917	0.887	0.811	0.710	0.561
	D6	0.885	0.855	0.780	0.678	0.530
	D7	0.838	0.804	0.729	0.628	0.481
P2	D1	0.944	0.915	0.838	0.736	0.588
	D2	0.934	0.904	0.828	0.726	0.578
	D3	0.915	0.885	0.810	0.708	0.559
	D4	0.891	0.861	0.785	0.684	0.537
	D5	0.861	0.831	0.756	0.654	0.508
	D6	0.829	0.799	0.724	0.623	0.477
	D7	0.779	0.750	0.675	0.574	0.427
P3	D1	0.867	0.837	0.761	0.660	0.513
	D2	0.857	0.827	0.751	0.650	0.503
	D3	0.837	0.808	0.732	0.631	0.485
	D4	0.814	0.784	0.709	0.608	0.461
	D5	0.785	0.755	0.680	0.579	0.433
	D6	0.753	0.723	0.648	0.548	0.402
	D7	0.702	0.674	0.598	0.498	0.353
P4	D1	0.714	0.685	0.610	0.510	0.365
	D2	0.703	0.675	0.599	0.499	0.354
	D3	0.685	0.656	0.581	0.481	0.337
	D4	0.661	0.632	0.557	0.458	0.313
	D5	0.632	0.604	0.528	0.429	0.285
	D6	0.601	0.572	0.497	0.399	0.254
	D7	0.551	0.522	0.449	0.350	0.207
P5	D1	0.468	0.439	0.365	0.267	0.125
	D2	0.457	0.428	0.355	0.257	0.114
	D3	0.439	0.410	0.337	0.239	0.097
	D4	0.416	0.387	0.314	0.216	0.074
	D5	0.387	0.358	0.285	0.188	0.047
	D6	0.356	0.327	0.255	0.159	0.017
	D7	0.308	0.279	0.207	0.111	–0.030

from: Rosser et al, Index of health-related quality of life in Hopkins A, *Measures of the quality of life* 1992, Royal College of Physicians

Appendix 8 - EQ-5D (EuroQoL)

EuroQol EQ-5
A brief overview

What is EQ-5D?

EQ-5D is a measure of health status developed for use in evaluating health and healthcare. It produces a numeric score for health status on which full health has a value of 1 and death has a value of 0. EQ-5D was developed by an international research group (see EuroQol Group below).

EQ-5D describes health status in terms of 5 dimensions

- Mobility
- Self care
- Usual activity
- Pain/discomfort
- Anxiety/depression

Each dimension is divided into 3 levels

- 1 – no problem
- 2 – some problem
- 3 – extreme problem

By combining different levels from each dimension, EQ-5D defines a total of 243 health states.

In the UK, the relative importance of each level/dimension is known from the results of a national survey of the general population commissioned by the Department of Health in 1993.

How is EQ-5D data collected?

A short 3-page questionnaire is completed by patients themselves. The questionnaire takes about a minute to fill in.

The questionnaire records

(a) the level of problems (if any) on each of the 5 dimensions
(b) the patient's rating of their overall health status using a 'thermometer'-like scale, marked 0 – 100
(c) minimal background information on the patient (this can be omitted if it duplicates pre-existing information)

What kind of information does EQ-5D produce?

EQ-5D generates 3 types of data for each patient

(a) a profile, indicating the extent of problems across the 5 dimensions
(b) a weighted health index, based on population values obtained from the 1993 survey
(c) a score on the self-rated 'thermometer', indicating the patient's own assessment of their health state

Examples of the type of information produced from EQ-5D are given in the User Guide.

Age/sex norms have been established for the general population in national surveys conducted in 1993 and replicated in 1995/96.

Comparative data are available from a range of clinical studies conducted in the UK and internationally.

What is EQ-5D being used for?

As an integral part of clinical practice, in monitoring health status of individual patients.

In the evaluation and audit of health care, by measuring changes in health status in individual patients, and in groups of patients.

Establishing levels of population health status both locally and nationally.

Comparison of health status in local communities and practice catchment areas, with national patterns.

In the UK, a NHS Task Group has been set up to co-ordinate the testing of EQ-5D as an outcome measure for use by clinicians and managers.

How is EQ-5D obtained?

EQ-5D is in the public domain, and save for commercial users, there is no fee for its use.

Within the UK, advice and support on the use of EQ-5D can be obtained from several sources, including the Centre for Health Economics, University of York (see contact details below).

Copies of the EQ-5D questionnaire can be obtained from the Centre, together with an abbreviated User Guide. Both are supplied free on request.

International enquiries may also be directed to the EuroQol Group's administrative office in Rotterdam, who can also supply copies of a more comprehensive User Guide.

What is the EuroQol Group?

Set up in 1987, the EuroQol Group is an international network of researchers from different disciplines, including medicine, psychology and economics.

Membership of the Group is open to those who contribute to the further development of EQ-5D, and to investigators with direct experience of its use.

A small administrative office in Rotterdam provides support for the network, and co-ordinates links with external agencies.

EQ-5D is in use in most countries around the world, and has been translated into all major languages. The Group oversees that translation process.

How is the EuroQol Group funded?

Individual researchers contribute a nominal sum for annual membership.

Where commercial interests are involved, a user fee may apply. Contact the Rotterdam office for details. Bids for European funding have been submitted.

Individual members of the EuroQol Group are free to act as consultants in advising on the use of EQ-5D, but may charge accordingly for their services.

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EQ-5D Index

Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes you own health state today.

Do not tick more than one box in each group.

Mobility

I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-Care

I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash of dress myself

Usual Activities (e.g. Work, study, housework, family or leisure activities)

I have no problem with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/Discomfort

I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/Depression

I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Estimated weights for EQ-5D health states

1 1 1 1 1	1.000	1 2 3 3 2	-0.005	2 1 3 2 3	0.128
1 1 1 1 2	0.848	1 2 3 3 3	-0.170	2 1 3 3 1	0.101
1 1 1 1 3	0.414	1 3 1 1 1	0.436	2 1 3 3 2	0.030
1 1 1 2 1	0.769	1 3 1 1 2	0.365	2 1 3 3 3	-0.135
1 1 1 2 2	0.725	1 3 1 1 3	0.200	2 2 1 1 1	0.746
1 1 1 2 3	0.291	1 3 1 2 1	0.313	2 2 1 1 2	0.675
1 1 1 3 1	0.264	1 3 1 2 2	0.242	2 2 1 1 3	0.241
1 1 1 3 2	0.193	1 3 1 2 3	0.077	2 2 1 2 1	0.623
1 1 1 3 3	0.028	1 3 1 3 1	0.050	2 2 1 2 2	0.552
1 1 2 1 1	0.883	1 3 1 3 2	-0.021	2 2 1 2 3	0.118
1 1 2 1 2	0.812	1 3 1 3 3	-0.186	2 2 1 3 1	0.091
1 1 2 1 3	0.378	1 3 2 1 1	0.400	2 2 1 3 2	0.020
1 1 2 2 1	0.760	1 3 2 1 2	0.329	2 2 1 2 3	-0.145
1 1 2 2 2	0.689	1 3 2 1 3	0.164	2 2 2 1 1	0.710
1 1 2 2 3	0.255	1 3 2 2 1	0.277	2 2 2 1 2	0.639
1 1 2 3 1	0.228	1 3 2 2 2	0.206	2 2 2 1 3	0.205
1 1 2 3 2	0.157	1 3 2 2 3	0.041	2 2 2 2 1	0.587
1 1 2 3 3	-0.008	1 3 2 3 1	0.014	2 2 2 2 2	0.516
1 1 3 1 1	0.556	1 3 2 3 2	-0.057	2 2 2 2 3	0.082
1 1 3 1 2	0.485	1 3 2 3 3	-0.222	2 2 2 3 1	0.055
1 1 3 1 3	0.320	1 3 3 1 1	0.342	2 2 2 3 2	-0.016
1 1 3 2 1	0.433	1 3 3 1 2	0.271	2 2 2 3 3	-0.181
1 1 3 2 2	0.362	1 3 3 1 3	0.106	2 2 3 1 1	0.383
1 1 3 2 3	0.197	1 3 3 2 1	0.219	2 2 3 1 2	0.312
1 1 3 3 1	0.170	1 3 3 2 2	0.148	2 2 3 1 3	0.147
1 1 3 3 2	0.09	1 3 3 2 3	-0.017	2 2 3 2 1	0.260
1 1 3 3 3	-0.066	1 3 3 3 1	-0.044	2 2 3 2 2	0.189
1 2 1 1 1	0.815	1 3 3 3 2	-0.115	2 2 3 2 3	0.024
1 2 1 1 2	0.744	1 3 3 3 3	-0.280	2 2 3 3 1	-0.003
1 2 1 1 3	0.310	2 1 1 1 1	0.850	2 2 3 3 2	-0.074
1 2 1 2 1	0.692	2 1 1 1 2	0.779	2 2 3 3 3	-0.239
1 2 1 2 2	0.621	2 1 1 1 3	0.345	2 3 1 1 1	0.367
1 2 1 2 3	0.187	2 1 1 2 1	0.727	2 3 1 1 2	0.296
1 2 1 3 1	0.160	2 1 1 2 2	0.656	2 3 1 1 3	0.131
1 2 1 3 2	0.089	2 1 1 2 3	0.222	2 3 1 2 1	0.244
1 2 1 3 3	-0.076	2 1 1 3 1	0.195	2 3 1 2 2	0.173
1 2 2 1 1	0.779	2 1 1 3 2	0.124	2 3 1 2 3	0.008
1 2 2 1 2	0.708	2 1 1 3 3	-0.041	2 3 1 3 1	-0.019
1 2 2 1 3	0.274	2 1 2 1 1	0.814	2 3 1 3 2	-0.090
1 2 2 2 1	0.656	2 1 2 1 2	0.743	2 3 1 3 3	-0.255
1 2 2 2 2	0.585	2 1 2 1 3	0.309	2 3 2 1 1	0.331
1 2 2 2 3	0.151	2 1 2 2 1	0.691	2 3 2 1 2	0.260
1 2 2 3 1	0.124	2 1 2 2 2	0.620	2 3 2 1 3	0.095
1 2 2 3 2	0.053	2 1 2 2 3	0.186	2 3 2 2 1	0.208
1 2 2 3 3	-0.112	2 1 2 3 1	0.159	2 3 2 2 2	0.137
1 2 3 1 1	0.452	2 1 2 3 2	0.088	2 3 2 2 3	-0.028
1 2 3 1 2	0.381	2 1 2 3 3	-0.077	2 3 2 3 1	-0.055
1 2 3 1 3	0.216	2 1 3 1 1	0.487	2 3 2 3 2	-0.126
1 2 3 2 1	0.329	2 1 3 1 2	0.416	2 3 2 3 3	-0.291
1 2 3 2 2	0.258	2 1 3 1 3	0.251	2 3 3 1 1	0.273
1 2 3 2 3	0.093	2 1 3 2 1	0.364	2 3 3 1 2	0.202
1 2 3 3 1	0.066	2 1 3 2 2	0.293	2 3 3 1 3	0.037

2 3 3 2 1	0.150	3 1 3 3 3	-0.380	3 3 1 2 2	-0.072
2 3 3 2 2	0.079	3 2 1 1 1	0.232	3 3 1 2 3	-0.237
2 3 3 2 3	-0.086	3 2 1 1 2	0.161	3 3 1 3 1	-0.264
2 3 3 3 1	-0.113	3 2 1 1 3	-0.004	3 3 1 3 2	-0.335
2 3 3 3 2	-0.184	3 2 1 2 1	0.109	3 3 1 3 3	-0.500
2 3 3 3 3	-0.349	3 2 1 2 2	0.038	3 3 2 1 1	0.086
3 1 1 1 1	0.336	3 2 1 2 3	-0.127	3 3 2 1 2	0.015
3 1 1 1 2	0.265	3 2 1 3 1	-0.154	3 3 2 1 3	-0.150
3 1 1 1 3	0.100	3 2 1 3 2	-0.225	3 3 2 2 1	-0.037
3 1 1 2 1	0.213	3 2 1 3 3	-0.390	3 3 2 2 2	-0.108
3 1 1 2 2	0.142	3 2 2 1 1	0.196	3 3 2 2 3	-0.273
3 1 1 2 3	-0.023	3 2 2 1 2	0.125	3 3 2 3 1	-0.300
3 1 1 3 1	-0.050	3 2 2 1 3	-0.040	3 3 2 3 2	-0.371
3 1 1 3 2	-0.121	3 2 2 2 1	0.073	3 3 2 3 3	-0.536
3 1 1 3 3	-0.286	3 2 2 2 2	0.002	3 3 3 1 1	0.028
3 1 2 1 1	0.300	3 2 2 2 3	-0.163	3 3 3 1 2	-0.043
3 1 2 1 2	0.229	3 2 2 3 1	-0.190	3 3 3 1 3	-0.208
3 1 2 1 3	0.064	3 2 2 3 2	-0.261	3 3 3 2 1	-0.095
3 1 2 2 1	0.177	3 2 2 3 3	-0.426	3 3 3 2 2	-0.166
3 1 2 2 2	0.106	3 2 3 1 1	0.138	3 3 3 2 3	-0.331
3 1 2 2 3	-0.059	3 2 3 1 2	0.067	3 3 3 3 1	-0.358
3 1 2 3 1	-0.086	3 2 3 1 3	-0.098	3 3 3 3 2	-0.429
3 1 2 3 2	-0.157	3 2 3 2 1	0.015	3 3 3 3 3	-0.594
3 1 2 3 3	-0.322	3 2 3 2 2	-0.056		
3 1 3 1 1	0.242	3 2 3 2 3	-0.221		
3 1 3 1 2	0.171	3 2 3 3 1	-0.248		
3 1 3 1 3	0.006	3 2 3 3 2	-0.319		
3 1 3 2 1	0.119	3 2 3 3 3	-0.484		
3 1 3 2 2	0.048	3 3 1 1 1	0.122		
3 1 3 2 3	-0.117	3 3 1 2 2	0.051		
3 1 3 3 1	-0.144	3 3 1 1 3	-0.114		
3 1 3 3 2	-0.215	3 3 1 2 1	-0.001		

Unconscious (-0.402)
Note: this value is the mean observed score. It does not result from the regression model.

Source: A1 TARIFF BASED ON UK SURVEY(1993)

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