CLASSIFICATION OF ANALOGUES OF SILDENAFIL, VARDENAFIL AND TADALAFIL

Submission to the Medicines Classification Committee for the 41st MCC meeting

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Annexes:

1. New Zealand data sheet for Viagra® (sildenafil citrate)
2. Chemical structures of some of the known analogues
3. Director General Statement on erectile dysfunction/sexual enhancement 'herbal' products (8 August 2008)
4. Summary of actions taken by overseas regulators in 2008

1. REASON FOR REQUEST

Medsafe is concerned about the risks posed to consumers of herbal products that contain structural analogues of the prescription medicines sildenafil, vardenafil and tadalafil, which are used in the treatment of erectile dysfunction (ED). Products containing these analogues are marketed as being natural and safe but they pose a high risk of harm to consumers who are unwittingly taking pharmacologically active derivatives of prescription medicines. Such consumers are unaware of the risk of interactions with other commonly used medicines and of the potential for serious adverse effects to occur, including loss of vision and hearing, hypotension, and death.

At present, manufacturers can legally include these analogues in dietary supplements in New Zealand. Scheduling of these analogues as prescription medicines would allow regulatory action to be taken against the manufacturers and/or suppliers of such products under the Medicines Act 1981.

2. BACKGROUND

Herbal medicines for the treatment of erectile dysfunction (ED) are regularly imported into New Zealand, either for personal use or for retail sale. Despite being labelled as containing only herbal ingredients, a number of these products have been tested and found to contain analogues of the prescription medicines sildenafil, tadalafil and vardenafil as undeclared ingredients. These analogues appear to be used in an effort to evade detection by regulatory agencies and, consequently, the actual analogues used are likely to change over time as regulators develop test methods to detect and rapidly screen for known analogues.

Medsafe regularly receives alerts from agencies such as the US FDA and Health Canada advising of herbal products containing analogues of sildenafil, tadalafil and vardenafil. Medsafe's Investigation and Enforcement Team have identified three

products available on the New Zealand market that were identified by the US FDA as containing a sildenafil analogue. These products have been sold from 'adult' shops and over the internet. A joint ESR/Medsafe project undertaken in September 2007 identified a further five products seized at the border that contained analogues of PDE-5 inhibitors.

3. CHEMISTRY OVERVIEW

A significant number of analogues of sildenafil, vardenafil and tadalafil exist, many of which were first described in the patent literature. The syntheses of the majority of these analogues are also described in detail in the patent literature. Annex 2 depicts chemical structures of some of the known analogues.

As Annex 2 shows, a large number of different sildenafil analogues have been synthesised. Modifications with respect to the sildenafil structure are focused on three areas of the molecule:

- the piperazine moiety, comprising a number of piperidine-type derivatives and/or changes in substitution around the piperazine ring eg. from *N*-methyl to *N*-ethoxy or *N*-ethyl, or methylation.
- the sulfonyl group – substitution with a carbonyl group.
- the carbonyl group – substitution of the pyrimidone carbonyl with a sulfonyl group.

Vardenafil analogues are fewer in number but modifications focus on two areas of the molecule, namely the piperazine moiety and the sulfonyl group.

The only tadalafil analogue identified to date is amino-tadalafil, in which the *N*-acetyl group has been replaced by a reactive hydrazone moiety. In contrast with other analogues, this analogue does not appear in the patent literature for tadalafil (Orme et al. 2002). Venhuis et al. (2007) postulated this may have been due to concerns over its reactivity.

It is worth noting that the synthesis of both the sildenafil and vardenafil analogues is relatively straightforward. Both routes involve convergent syntheses, bringing together two halves of the molecule towards the end of the synthesis. One of the key sildenafil intermediates is reported to be readily available from speciality Asian chemical suppliers (Venhuis et al. 2007). Tadalafil analogues can also easily be produced, in a four step linear synthesis starting from an amino acid such as tryptophan (Orme et al. 2002). From a chemistry perspective, this means that the production of new analogues is relatively straightforward (Venhuis et al. 2007).

4. NEW ZEALAND EXPERIENCE

4.1 Products in New Zealand and their regulatory status

In New Zealand, products containing analogues of sildenafil, tadalafil and vardenafil can legally be marketed as dietary supplements under the Dietary Supplements Regulations 1985.

A joint Environmental Science and Research (ESR)/Medsafe project undertaken in September 2007 identified five products seized at the border that were found to contain analogues of PDE-5 inhibitors (Table 1 below).

Table 1: *Summary of ESR Test Results for Products Seized at the Border*

Product Name	Analogue identified	Quantity
Product A	Homosildenafil	19 mg/capsule
Product B	Aminotadalafil	29.5 mg/capsule
Product C	Hydroxyhomosildenafil	1 mg/capsule
Product D	Hydroxyhomosildenafi	1 mg/capsule

The quantities present in these products vary significantly and this is a reflection of the fact that these products are likely to be manufactured under conditions that do not comply with principles of Good Manufacturing Practice. It is worth noting that tadalafil in New Zealand approved medicines is only available in 10 mg and 20 mg strengths (with a maximum recommended daily dose of 20 mg) and that, as such, the aminotadalafil content exceeds the upper dose level by 47.5%. Section 6.2.2 discusses the likely risk profile of aminotadalafil.

Three products identified by overseas regulators as containing thiomethisosildenafil (Rize 2 The Occasion, Rose 4 Her and Viapro) were also found to be marketed in New Zealand by Medsafe's Investigation and Enforcement Team. In addition, a further group of approximately 20 products believed to contain analogues have been collected during border surveillance activities and await testing by ESR.

The Investigation and Enforcement Team at Medsafe have also identified a number of other products being sold in New Zealand that are believed to contain sildenafil, tadalafil and vardenafil analogues. These products are available to New Zealand consumers in retail shops such as 'adult' shops, and over the internet.

4.2 Actions taken by Medsafe

On 8 August 2008, the Director General of Health issued a statement under Section 98 of the Medicines Act 1981 warning consumers about three products tested and found to contain an analogue of sildenafil (see Annex 3). This was based on information from the US FDA, which had tested these products and they were recalled after they were found to contain thiomethisosildenafil (also known as sulfo-homosildenafil). The affected products were 'Rize 2 The Occasion', 'Rose for Her' and 'Viapro'.

5. INTERNATIONAL EXPERIENCE

5.1 Classification in other countries

5.1.1 Australia

Sildenafil, vardenafil and tadalafil are listed in Schedule 4 in the Standard for the Uniform Scheduling of Drugs and Poisons No. 23 (SUSDP 23). They are therefore scheduled as prescription medicines in Australia.

Analogues of sildenafil, vardenafil and tadalafil are not currently included in any of the schedules of the SUSDP 23. Further, since all ingredients used in low risk medicines in Australia must be included in the "list of substances approved for use in low risk medicines", medicines in Australia cannot legally contain these analogues. As products containing analogues of sildenafil, tadalafil or vardenafil would be

captured under the definition of a medicine in Australia, these products would be regarded as unlicensed medicines.

5.1.2 US and Canada

In the US, analogues of sildenafil, vardenafil and tadalafil are classed as unapproved new drugs.

Products containing analogues of sildenafil, vardenafil and tadalafil are regarded as unauthorized drug products in Canada.

5.2 Regulatory action taken in other countries

Since the beginning of 2007 Medsafe has received alerts of 42 herbal medicines identified as containing analogues of sildenafil, vardenafil or tadalafil (as at 4 Sept 2008). Annex 4 contains a summary of the warnings, alerts and advisory statements issued by overseas regulators in 2008, from 1 January 2008 to 19 September 2008.

5.3 Products found to contain analogues in other countries

A significant number of analogues of sildenafil, vardenafil and tadalafil have been identified in dietary supplements marketed for sexual enhancement and the literature contains a growing number of reports describing the isolation and characterisation of such analogues. Analytical strategies to detect analogues are improving (Singh et al. 2009). In a recent survey of 26 herbal aphrodisiac products available over-the-counter from pharmacies and convenience stores in Hong Kong, 14 (54%) were found to contain analogues of sildenafil or vardenafil (Poon et al. 2007).

Analogues recently isolated and characterised from dietary supplements include thioquinapiperifil (Uchiyama et al. 2008), benzamidenafil (Zou et al. 2008), methisosildenafil (Reepmeyer et al, 2007), piperidino vardenafil and acetildenafil (Park et al. 2007), a new vardenafil analogue (Lam et al. 2007), and the thio-analogues, thiohomosildenafil and thiosildenafil (Zou et al. 2008).

A summary of the products in which an analogue of sildenafil, tadalafil or vardenafil has been identified by an overseas regulatory authority is given in the table below.

Table 2: *Analogues Detected in Products by Overseas Regulatory Authorities*

Analogue identified	**Product**
Hydroxyhomosildenafil	Boy Joy, Libido Forte, Tian Li, Virility Power (VIP), Xiadafil VIP
Sildenafil analogue (unidentified/unspecified)	Aspire lite, Aspire 36, Blue Steel, China Vigour, Enhancex Her and Him, Hero, Nasutra, Oyster Extract, Powertabs, Shangai Ultra X, 4Everon
Methisosildenafil	Libido Extension, Rose 4 Her
Thiomethisosildenafil	Rize 2 The Occasion, Viapro
Thione analogue of sildenafil	True Mans Sexual Energy Nutrient
Aminotadalafil	Dr Life, Encore, Rhino Max
Tadalafil analogue (unidentified/unspecified)	Bell Magnum Bullet, Sweet

	Energiser Vitality Candy
Piperidino vardenafil	H.S. Joy of Love, Satis 60hrs Everlasting Formula, Jolex
Vardenafil analogue	Libidus, Vigor 25
Acetildenafil and piperidino vardenafil	Onyo
Sildenafil or a sildenafil analogue (see Note 1)	Actra-Sx, Adam Free, Armstrong, Natural Herbal Supplement, Lady Shangai, Naturale Super Plus, NaturalUp, Shangai Regular, Yilishen
Piperidino vardenafil, hydroxyacetildenafil, acetildenafil and/or hydroxyhomosildenafil (see Note 2)	Enhanix, New Extra, Men's Formula, Erextra, Power 58 Extra, Platinum Power Extra, Stretch Up, Valentino

Note 1 – This group of products were shown to contain sildenafil or a sildenafil analogue (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_106-eng.php)

Note 2 – This group of products were shown to contain piperidino vardenafil, hydroxyacetildenafil, acetildenafil and/or hydroxyhomosildenafil (http://www.dh.gov.hk/english/press/2007/070227_3.html)

As products containing analogues are manufactured under conditions that are unlikely to comply with principles of Good Manufacturing Practice for pharmaceuticals, the quantities present in products vary considerably.

Where quantities have been determined in products, most are considered to be pharmacologically relevant (Venhuis et al. 2008a). In the literature, acetildenafil has been reported at 60 mg/capsule; hydroxyethylsildenafil at 40 mg/capsule; piperidino vardenafil at 8 mg/capsule (Venhuis et al. 2008a); thiohomosildenafil at 55 mg/capsule (Venhuis et al. 2008b) and 67 mg/capsule (Zou et al. 2008); thioquinapiperifil at 13-15 mg/tablet (Uchiyama et al. 2008); thiosildenafil at 0.4 mg/tablet (Uchiyama et al. 2008); benzamidenafil at 25 mg/capsule (Zou et al. 2008) and thiosildenafil at 35 mg/capsule (Zou et al. 2008).

In comparison, doses in sildenafil tablets approved in New Zealand are 25 mg, 50 mg and 100 mg with a maximum recommended daily dose (MRDD) of 100 mg/day. For vardenafil, tablets are available in 5, 10 and 20 mg strengths (MRDD of 20 mg). Tadalafil is available in 10 mg and 20 mg strengths (MRDD of 20 mg).

6. CLINICAL EXPECTATIONS

6.1 Pharmacology of sildenafil, vardenafil and tadalafil

The prescription medicines sildenafil, tadalafil and vardenafil are potent, selective and reversible inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5), the enzyme which catalyses the degradation of cGMP in vascular smooth muscle.

Nitric oxide activates guanylyl cyclase, the enzyme which catalyses the conversion of guanosine triphosphate (GTP) to cGMP, leading to relaxation of vascular smooth muscle in the corpus cavernosum. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, PDE-5 inhibition results in increased corpus

cavernosal levels of cGMP. The pathways involved in NO/cGMP activation are summarised in the figure below (from Rosen & Kostis, 2003).

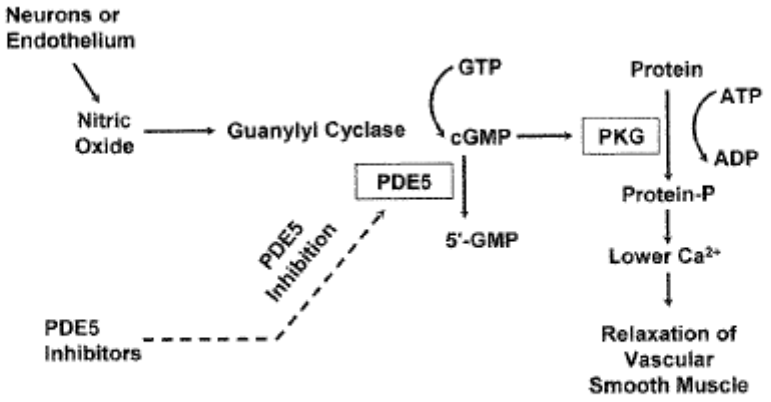

FIGURE 1. Nitric oxide–cyclic guanosine monophosphate (cGMP) signaling in cavernous smooth muscle. ADP = adenosine diphosphate; ATP = adenosine triphosphate; GTP = guanosine triphosphate; PDE = phosphodiesterase; PKG = protein kinase G. (Adapted with permission from *J Biol Chem.*[2])

PDE-5 inhibitors also increase cGMP levels within vascular and visceral smooth muscle cells resulting in vasodilation. PDE-5 is also found in platelets and enhanced platelet anti-aggregatory activity has been observed *in vitro*.

6.2 Safety pharmacology and toxicology

6.2.1 Parent compounds

There are 11 families of mammalian PDEs identified, characterised in terms of their respective substrate specificities and tissue distribution. In the penile corpora the degradation of cGMP is catalysed primarily by PDE-5. The localisation and assumed role of the best characterised of these enzymes, PDE-1 to PDE-6, are summarised in the table below.

Table 3: *Summary of PDE Functions (from Michelakis et al. 2000)*

Subtype	Substrate	IC_{50} of sildenafil,* nmol/L	Localization†
PDE1	cGMP and cAMP‡	280	Heart, brain, kidney, liver, skeletal muscle, visceral and vascular smooth muscle
PDE2	cGMP and cAMP	68 000	Adrenal cortex, brain, corpus cavernosum, heart, liver, kidney, visceral smooth muscle, skeletal muscle
PDE3	cAMP	16 200	Heart, corpus cavernosum, platelets, vascular and viscera smooth muscle, liver, kidney
PDE4	cAMP	7 200	Kidney, lung, mast cells, heart, skeletal muscle, vascular and visceral smooth muscle
PDE5	cGMP	3.5	Corpus cavernosum, platelets, skeletal muscle, vascular and visceral smooth muscle
PDE6	cGMP	34–38	Retina (cone and rod cells)

Note: cGMP = cyclic guanosine monophosphate, cAMP = cyclic adenosine monophosphate, IC_{50} = concentration at which 50% inhibition occurs.
*Data from Wallis and colleagues.[3]
†In descending order of concentration.
‡PDE1 has a greater affinity for cGMP than for cAMP.

The relative selectivity of sildenafil, tadalafil and vardenafil towards other PDE enzymes is well studied, and these data are summarised in the table below (Rosen &

Kostis, 2003). This high degree of selectively is the result of rational drug design to optimise PDE-5 inhibition and minimise inhibition of other (i.e. off-target) PDEs.

Table 4: *PDE Selectivity of Sildenafil, Tadalafil and Vardenafil (from Rosen & Kostis, 2003)*

	Sildenafil 25–100 mg	Tadalafil 20 mg	Vardenafil 10–20 mg
PDE5 Selectivity ratio*			
PDE1	>80	>10,000	>130
PDE2	>1,000	>10,000	>1,000
PDE3	~4,000	>10,000	>1,000
PDE4	>1,000	>10,000	>1,000
PDE5	1	1	1
PDE6	10	~700	>15
Pharmacokinetics			
IC_{50} for PDE5 (nmol/L)	3.5–3.9	0.94	0.7
t_{max} (hr)	~1	2.0	0.9–0.7
$t_{1/2}$ (hr)	4	17.5	4.2–3.9
C_{max}	127–560 ng/mL	378 µg/L	9.05–20.9 µg/L

C_{max} = maximum concentration; IC_{50} for PDE5 = concentration of drug needed to inhibit 50% of PDE5; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration.

*The ratio of the agent's selectivity for PDE5 vs a particular PDE. For each agent, PDE5 is the comparator. The higher the selectivity ratio for a PDE5 inhibitor, the more potent its effects on PDE5 relative to a given PDE (see Table 1 for PDE locations).

Adapted from *Physician's Desk Reference*,[11] *Am J Cardiol*,[12] *Int J Impot Res*,[13,17,18] *World J Urol*,[14] European Public Assessment Report,[15,19] and *Eur Urol*.[16]

It is generally accepted that the visual disturbances associated with high doses (≥100mg) of sildenafil and vardenafil arise from PDE-6 inhibition as this enzyme is involved in the phototransduction cascade of the retina where cGMP confers colour vision (Michelakis et al. 2000). Visual symptoms consist of mild and transient (<24 h) differences in blue/green colour discrimination.

PDE-3 is the cAMP-specific PDE involved in the control of cardiac contractility. Side effects of sildenafil, vardenafil and tadalafil reported to arise from inhibition of PDE-3 include inhibition of platelet aggregation and increased heart rate (Eros et al. 2008). Sildenafil has an approximately 4000-fold selectivity for PDE-5 over PDE-3 (Michelakis et al. 2000).

Other side effects which are considered likely to be due to PDE-5 inhibition include gastrointestinal effects such as dyspepsia (PDE-5 inhibition in visceral smooth muscle and relaxation of the lower oesophageal sphincter resulting in reflux), headache, flushing and rhinitis (i.e. vasodilatory effects) (Michelakis et al. 2000).

Sudden decrease or loss of hearing has been described in close temporal association with PDE-5 inhibitors. In May 2008, the New Zealand Medicines Adverse Reactions Committee (MARC) recommended that the datasheets for all PDE-5 inhibitors be updated to provide information warning prescribers of the potential risk of sudden hearing loss associated with PDE-5 inhibitors, and what action to take should sudden hearing loss occur.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been observed in close temporal association with the use of PDE-5 inhibitors, including decreased vision and this condition can result in a permanent loss of vision. At risk groups for NAION are those >50 years, and those with risk factors such as high blood pressure, high cholesterol, diabetes, smoking, or those with a blood vessel problem in the eye that can lead to stroke.

Sildenafil can cause migraine and, because it activates the serotonin transformer (SERT) in the CNS which stimulates serotonin uptake, certain side effects including dizziness, depression, insomnia, anxiety and aggression are considered to be associated with SERT stimulation (Eros et al. 2008).

Pharmacokinetic interactions have been demonstrated in clinical studies with PDE-5 inhibitors. Sildenafil, vardenafil and tadalafil are metabolised predominantly by hepatic CYP3A4, and their co-administration with potent CYP3A4 inhibitors such as erythromycin and ritonavir have been shown to produce large increases in their plasma levels.

Hypotensive effects known to occur with PDE-5 inhibitors are a result of the vasodilatory effect of PDE-5 inhibitors. In New Zealand, sildenafil is approved to treat patients with symptom-limited pulmonary arterial hypertension to improve exercise capacity. Sildenafil increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to selective vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation (Revatio® data sheet). PDE-5 inhibitors are known to potentiate the hypotensive effects of acute and chronic nitrates. As such, the concomitant use of glyceryl nitrate, isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil and organic nitrates is contraindicated with PDE-5 inhibitors. Further, the use of alpha- blockers is contraindicated with vardenafil as it may lead to symptomatic hypotension (Levitra® data sheet).

The use of PDE-5 inhibitors is contraindicated in patients with a history of stroke or myocardial infarction; serious cardiovascular events (including death) have been associated with PDE-5 use.

The New Zealand data sheets for sildenafil (Annex 1), tadalafil and vardenafil warn prescribers of these risks.

Any compounds possessing PDE-5 inhibitory activity are likely to share the same risk profile as the known PDE-5 inhibitors.

6.2.2 Analogues

Limited data exist regarding the biological activities of the analogues of sildenafil, vardenafil and tadalafil. Such biological activities are limited to *in vitro* PDE-5 and PDE-6 inhibition studies. Because the analogues have not been subject to regulatory assessment of their safety and efficacy, pre-clinical data in the form of safety pharmacology and toxicology studies and clinical trial data are not available. The *in vitro* data that are available for the analogues that have been detected in dietary supplements are summarised in the table below. It is apparent from these data that analogues do possess PDE-5 inhibitory activity, in some cases at levels significantly higher than the corresponding parent compound.

Table 5: *PDE Selectivity of Sildenafil, Tadalafil and Vardenafil and Analogues*

Compound	PDE-5 Inhibition (IC_{50})	Relative Potency*	PDE-6 Inhibition (IC_{50})	Relative Potency*
Sildenafil	6.6 nM [Saenz de Tejada et al. 2001] 7.1 nM [Venhuis et al. 2007] 6.86 nM [Kim et al. 2002] Ki 7.2 mM [Hirose et al. 2004] 3.6 nM [Antunes et al. 2008] 4.3 nM [Zou et al. 2008]	1	15 nM [Zou et al. 2008]	1
Benzamidenafil	1.1 nM [Zou et al. 2008]	0.26	20 nM [Zou et al. 2008]	1.33
Hydroxyhomosildenafil	1.9 nM [Antunes et al. 2008] 3.4 nM [Venhuis et al. 2007]	0.52 0.48		
Piperidino sildenafil	5.8 nM [Antunes et al. 2008]	1.6		
Thioquinapiperifil	Ki 0.16 mM [Hirose et al. 2001]	0.02		
Acetildenafil	7.6 nM [Venhuis et al. 2007]	1.1	Cited as a PDE-6 inhibitor [Venhuis et al. 2007]	
Homosildenafil	3.8 nM [Venhuis et al. 2007]	0.53		
Thiosildenafil	0.59 nM [Kim et al. 2002]	0.09	60 nM [Kim et al. 2002]	4
Vardenafil	0.7 nM [Saenz de Tejada et al. 2001]	0.11		
Tadalafil	5.0 nM [Venhuis et al. 2007]	0.70		

* Potency relative to parent; values<1 are more potent than parent.
IC_{50} – concentration of drug required to inhibit the enzyme by 50%.
K_i – inhibition constant.

The patent literature (Kim et al. 2002) includes the inhibitory activities for a number of thiosildenafil analogues; PDE-5 IC_{50} values ranged from 0.40-0.62 nM, compared with 6.86 nM for sildenafil. It is apparent that the level of inhibition for thio-analogues is significantly increased relative to the parent PDE-5 inhibitor, sildenafil. For example, the K_i (a measure of the binding affinity of the substrate) for thioquinapiperifil towards PDE-5 (0.16 mM) is significantly higher than the parent sildenafil (K_i = 7.2 mM) and thiosildenafil is a significantly more potent inhibitor than sildenafil (IC_{50} of 0.59 nM vs 6.86 nM). Such differences are likely to result in clinical differences in the potency of the analogues. In support of this assertion, the recommended daily doses for tadalafil and vardenafil are lower than that of sildenafil, consistent with the increased *in vitro* inhibitory potency of the tadalafil and vardenafil towards PDE-5.

Information regarding the selectivity of the analogues with regard to their PDE inhibitory activities is scant. Benzamidenafil is reported to be a weak inhibitor of PDEs 1, 2, 3 and 4 but it showed potent inhibitory activity towards PDE-6 (20 nM), similar to that of sildenafil (15 nM) (Zou et al. 2008). The patent of Kim et al. (2002) lists a number of thione analogues and their inhibitory activities towards PDE-1, 3, and 6; PDE1 IC_{50} values ranged from 10-2430 nM; PDE 3 from 1030-5630 nM; PDE 6 from 35-327 nM.

It is worth noting that *in vitro* biological activity is one factor in assessing the likely clinical effect of a pharmacologically active ingredient and that pharmacokinetic parameters also require consideration. Venhuis et al. (2007) considered that differences in pharmacokinetic parameters induced by structural modifications could produce marked differences in onset of action, blood levels, half-lives, brain penetration and metabolism, giving rise to very different risk profiles for analogues relative to the parent compound. The importance of pharmacokinetic differences is demonstrated by the enhanced permeability of vardenafil due to the presence of an extra (lipophilic) methylene group relative to sildenafil (Eros et al. 2008), presumably contributing to its more rapid clinical onset.

No toxicological data exist for the analogues and adverse drug reaction reports are limited to two reports (refer to section 6.3). Specific risks of potential toxicological significance have been identified. For example, the aminotadalafil analogue, which contains a reactive hydrazone group, has the potential to be able to bind to the active site of PDE-5 to irreversibly inhibit the enzyme (Venhuis et al. 2007). The piperidino vardenafil analogue lacks the primary target for metabolism (*N*-dealkylation; see Hyland et al. 2001; Walker et al. 1999; Muirhead et al. 2002) and is more lipophilic than vardenafil. This is predicted to result in its increased persistence in the body and penetration into the brain with possible neurotoxic sequelae (Venhuis et al. 2007). Acetildenafil has been reported as being a relatively unselective inhibitor with respect to PDE-5 and PDE-6 (Venhuis et al. 2007), raising the potential for ocular toxicity at doses that have been detected in products (60 mg/capsule).

6.2.3 Structure-activity relationships

The above data and other data found in the literature (Eros et al. 2008; Antunes et al. 2008) indicate that PDE-5 is tolerant to a variety of structural modifications to the parent PDE-5 inhibitors sildenafil, vardenafil and tadalafil, while still retaining inhibitory activity.

Computer modelling of the active site of PDE-5, including docking studies and prediction of pharmacokinetic and toxicology parameters, identified key residues in the active site important for hydrogen bonding and π–stacking with the ligand (Antunes et al. 2008). This highlighted the importance of hydrogen bonding in the active site.

Structural features identified as key factors in good binding with PDE-5 and the display of inhibitory activity included:

- A polar group at the sulfonylpiperazine nitrogen, which potentiates biological activity, attributed to a hydrophilic solvent interaction (Antunes et al. 2008). This

feature is present in the analogues hydroxyhomosidlenafil, hydroxyvardenafil, hydroxyacetildenafil as an *N*-ethoxy group.

- Hydrogen bonding with Gln817 and Tyr612 in the active site of PDE-5. An ethoxy group at C19 (sildenafil numbering) was shown to fulfil this role for Gln817 bonding. This structural motif is present in acetildenanfil, hydroxyacetildenafil, homosidlenafil, isobutylsildenafil, hydroxyhomosildenafil, aildenafil, piperidino sildenafil, thioaildenafil, thiohomosildenafil etc. Hydrogen bonding to Tyr612 was shown to occur via carbonyl groups such as those in the pyrimidinone moiety present in the parent PDE-5 inhibitors and their analogues. Biological activity data suggest substitution of the pyrimidone carbonyl for a sulfonyl-group increases the inhibitory activity i.e. thiosildenafil vs sildenafil.
- A π–stacking interaction with Phe820 in the PDE-5 active site and the fused rings, which are present in most of the PDE-5 inhibitors identified to date. It is reasonably anticipated that the analogue benzamidenafil, though lacking a fused ring, is still able to interact in this way via π-stacking with one of its aromatic rings.

The active site computer modelling studies on PDE-5 provide evidence that there is a significant degree of tolerance toward structural modifications to the parent inhibitors sildenafil, vardenafil and tadalafil to display the same, or more potent, biological inhibitory activities. The thio-sildenafil analogues are more potent inhibitors of PDE-5 (Kim et al. 2002). Amino-tadalafil, which contains the reactive hydrazone structural motif, is predicted to act as an irreversible inhibitor of PDE-5 and this may result in a significant prolongation of its pharmacological activity.

Key structural features identified for good enzyme-ligand binding are present in the analogues. Biological data for the analogues, though limited, also show biological activity is retained or increased by a diverse range of modifications in areas distal to the areas critical for good enzyme binding.

No information is available regarding whether any of the active ingredients currently approved for use in medicines in New Zealand are capable of significant PDE-5 inhibition. It is, however, considered that any compound possessing potent PDE-5 inhibitory activity is likely to share the same risk profile as the known PDE-5 inhibitors.

6.3 Clinical data including adverse reaction reports

No reports of clinical studies have been published for any of the analogues. While the efficacy of the analogues have not been described in the literature, it is reasonable to expect on the basis of the *in vitro* activities, that they are efficacious. It is worth noting that *in vitro* biological activities towards PDE-5 were used to exemplify the original patents for sildenafil, vardenafil and tadalafil as treatments for ED.

Adverse reactions associated with the consumption of herbal aphrodisiacs containing analogues have been reported in the literature. In Hong Kong, drug-induced ataxia was suspected in a 28 year old male who presented with unsteady gait and frequent falls after taking a product containing acetildenafil for eight consecutive days (Poon et al. 2008). In Japan, a case of impaired liver function was reported in an individual who consumed a product containing hydroxyhomosildenafil (cited in Blok-Tip et al. 2004).

A lack of formal adverse reaction reports does not however reflect an absence of adverse reactions. The use of herbal ED products may not be declared to health care practitioners and significant under-reporting may arise due to stigma associated with ED and the use ED products.

Clinically, based on the above data, it can be reasonably predicted that structural analogues of sildenafil, vardenafil and tadalafil will have the same primary pharmacological target and act as PDE-5 inhibitors. The available evidence suggests that some analogues are likely to be considerably more potent than the respective parent inhibitor and any loss of selectivity in PDE inhibition invoked by structural change may result in an increase in the severity of known off-target adverse effects including visual disturbances and effects on cardiac function.

7. RISK ASSESSMENT

The PDE-5 inhibitors sildenafil, tadalafil and vardenafil are classified as prescription medicines. On the basis of the available data, it is predicted that the primary pharmacological action of structural analogues of these compounds is the same i.e. potent PDE-5 inhibitors. Established risks around the use of PDE-5 inhibitors arising from PDE-5 inhibition include interactions with nitrates and hypotension. However, the analogues' selectivity with respect to other PDEs remains unquantified for most known analogues and this presents a significant risk to consumers in the case of off-target PDE inhibition, for example, inhibition of PDE-6 (visual disturbances) and PDE-3 inhibition (cardiac effects).

Structural analogues of sildenafil, vardenafil and tadalafil have not been assessed with respect to their toxicological and pharmacological properties, or in formal clinical studies. Although this lack of data means that the risks around the inclusion of analogues in herbal aphrodisiacs cannot be fully determined, the likelihood that they are potent PDE-5 inhibitors represents a high risk of harm to unwitting consumers, particularly those individuals with well-established risk factors for adverse reactions with PDE-5 inhibitors. This is in the context that individuals with risk factors may actively seek out a "natural" and "safe" herbal alternative to prescription medicines for ED, without the knowledge of their health care practitioner.

The risk of harm is considered to be higher than for the registered prescription medicines containing sildenafil, tadalafil and vardenafil not only because the safety profile of these analogues has not been established, but also because increases in potency and changes to the pharmacokinetic profile relative to the parent compounds means analogues may be present at supra-therapeutic levels. Further, a lack of pharmaceutical-type quality control standards in the manufacture of these products means significant variations in the quantity and/or quality of analogues are possible, compounding the risk of supra-therapeutic levels in products.

In summary, the significant risks posed by pharmacologically active derivatives of prescription medicines being available as General Sale warrants their classification as prescription medicines. Should data become available in the future which alters our knowledge about the risk:benefit profile of individual analogues, this classification can be re-visited on a case-by-case basis.

8. MEDSAFE RECOMMENDATIONS

Medsafe recommends that the First Schedule to the Medicines Regulations 1984 be amended as follows (new text shown in italics):

Sildenafil *and its analogues*
Tadalafil *and its analogues*
Vardenafil *and its analogues*
Phosphodiesterase type 5 inhibitors

This wording is intended to capture all known structural analogues of sildenafil, tadalafil and vardenafil, as well as any new analogues as they are discovered. This wording is also intended to capture any new compounds that are inhibitors of phosphodiesterase type 5.

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MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

INFORMATION FOR HEALTH PROFESSIONALS

Data Sheet

VIAGRA®

sildenafil citrate tablets (25 mg, 50 mg and 100 mg)

Presentation

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

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

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

In addition to sildenafil citrate, each VIAGRA tablet contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, glycerol triacetate, indigo carmine aluminium lake (CI 73015). VIAGRA tablets may contain PF0102.

Viagra tablets are presented in blister packs of 4 tablets.

Uses

Actions

Mechanism of action:

VIAGRA is an oral therapy for erectile dysfunction which restores impaired erectile function by increasing blood flow to the penis, resulting in a natural response to sexual stimulation.

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) which is responsible for degradation of cGMP in the corpus cavernosum. VIAGRA 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 cavernosal levels of cGMP. Therefore sexual stimulation is required in order for VIAGRA to produce its beneficial pharmacological effects.

Single oral doses of VIAGRA up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing 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.

VIAGRA has no effect on visual acuity or contrast sensitivity. Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using 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. In-vitro studies show that sildenafil is 10-fold less potent against PDE6 than PDE5.

Studies *in vitro* have shown that sildenafil has between 10 and 10,000-fold greater selectivity for PDE5 than for other phosphodiesterase isoforms (PDEs 1, 2, 3, 4 6, 7 to 11). 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.

Clinical Trials

The efficacy and safety of VIAGRA was evaluated in 21 randomised, double-blind placebo controlled trials of up to 6 months duration. VIAGRA was administered to more than 3,000 patients aged 19-87, with erectile dysfunction (ED) of various aetiologies (organic, psychogenic, mixed). The efficacy was evaluated by global assessment question, diary of erections, the International Index of Erectile Function (IIEF, a validated sexual function questionnaire) and a partner questionnaire.

VIAGRA efficacy, determined as the ability to achieve and maintain an erection sufficient for sexual intercourse, was demonstrated in all 21 studies and was maintained in long term extension studies (one year). 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 addition to improvements in erectile function, analysis of IIEF showed that VIAGRA treatment also improved the domains of orgasm, satisfaction with intercourse and overall satisfaction.

Across all trials, the proportion of patients reporting improvement on VIAGRA were 59% of diabetic patients, 43% of radical prostatectomy patients and 83% of patients with spinal cord injury (versus 16%, 15% and 12% on placebo respectively).

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 plethysmography (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.

Pharmacokinetics

Pharmacokinetic Properties

Absorption

Sildenafil is rapidly absorbed. Maximum 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%). The oral pharmacokinetics of sildenafil are proportional over the recommended dose range (25-100 mg).

When VIAGRA is taken with a high fat meal, 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%. Patients may need to individualise their dosing relative to their food intake based on their own experienced clinical response.

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 sixteen healthy volunteers receiving VIAGRA (100 mg single dose), the mean semen concentrations of sildenafil 1.5 and 4 hours post-dose were 18% and 17% respectively of the plasma concentration at the same time point. The amount in the ejaculate at 90 minutes after dosing was less than 0.0002% of the administered dose.

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 PDE selectivity profile similar to sildenafil and an in-vitro potency for PDE5 approximately 40% 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 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

Pharmacokinetics in Special Patient Groups:

Elderly

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in younger volunteers (18-45 years). However, analysis of the safety database showed that age had no effect on the incidence of adverse events.

Renal Insufficiency

In volunteers with mild (Cl_{cr} = 50-80 mL/min) and moderate (Cl_{cr} = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of VIAGRA (50 mg) were not altered. In volunteers with severe (Cl_{cr} = 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and C_{max} (88%) compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency

In volunteers with hepatic cirrhosis (Child-Pugh classification 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 severe hepatic impairment have not been studied.

Indications

VIAGRA is indicated for the treatment of erectile dysfunction in adult males.

Dosage and Administration

VIAGRA tablets are for oral administration.

Use in Adults

The recommended starting dose is 50 mg taken 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 **Pharmacokinetics**).

Use in The Elderly

Since sildenafil clearance is reduced in elderly patients, a first dose of 25 mg should be considered. 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 for **Use in Adults** should be followed for patients with mild to moderate renal impairment (Cl_{cr} = 30-80 mL/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (Cl_{cr} <30 mL/min) a 25 mg starting 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 starting dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients using other medications

Concomitant use of potent CYP 3A4 inhibitors has been associated with increased plasma levels of sildenafil (e.g. erythromycin, 182%, saquinavir, 210%). It can also be expected that more potent CYP 3A4 inhibitors such as ketoconazole and itraconazole would result in increased plasma levels of sildenafil. (See **Effects of other drugs on Viagra**). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Given the extent of the interaction with patients receiving concomitant therapy with ritonavir, it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48 hour period. (See **Effects of other drugs on Viagra**).

In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at lower doses should be considered (see **WARNINGS AND PRECAUTIONS** and **INTERACTIONS**).

Use in Children

VIAGRA is not indicated for use in children.

Contraindications

Use of VIAGRA is contraindicated in patients with known hypersensitivity to any component of the tablet.

VIAGRA was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its co-administration with nitric oxide donors, organic nitrates or organic nitrites in any form, either regularly or intermittently, is therefore contraindicated. Drugs which must not be used concomitantly include glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. (see **Warnings and Precautions**).

VIAGRA is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors (e.g. patients with severe cardiovascular disease such as established cardiac failure and unstable angina pectoris) (see **Warnings and Precautions**). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing VIAGRA.

VIAGRA is not recommended in patients with male erectile dysfunction with a previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (see Warnings and Precautions, Adverse Reactions - Post marketing data, Other events).*

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), hypertension (blood pressure >170/110 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).

Warnings and Precautions

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes and identify appropriate treatment.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, including those with recent onset angina, since there is a degree of cardiovascular risk associated with sexual intercourse. VIAGRA has vasodilator properties, resulting in mild and transient decreases in blood pressure and, as such, potentiates the hypotensive effect of nitrates (see Contraindications).

Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent

loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE-5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see Contraindications and Adverse Reactions - post marketing data).

After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered (see Contraindications). Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/ml (compared to peak plasma levels of approximately 440 ng/ml). In the following patients: age > 65, hepatic impairment (eg. cirrhosis), severe renal impairment (eg. creatinine clearance <30 ml/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (eg. erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.

In clinical trials, sildenafil has been shown to have systemic vasodilatory properties that result in transient decreases in blood pressure. This is of little or no consequence in most patients. However, prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

Agents for the treatment of erectile dysfunction 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 leukemia).

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

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals (see **INTERACTIONS**). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at lower doses should be considered (see **DOSAGE AND ADMINISTRATION**). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

VIAGRA has no effect on bleeding time, including during co-administration with aspirin. In-vitro studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of VIAGRA to patients with bleeding disorders or active peptic ulceration. Therefore VIAGRA should be administered with caution to these patients.

There are limited safety data in patients with diabetic retinopathy.

Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing patients should be advised to stop taking sildenafil and consult a physician promptly.

The incidence of adverse events may be greater in those patients who require the maximum recommended dose of 100 mg (e.g. some diabetic and spinal cord injury patients).

Patients with cardiovascular disease who have not engaged in sexual intercourse for a number of years should have their cardiovascular status carefully assessed prior to initiating treatment with VIAGRA.

Prolonged erections greater than four hours and priapism (painful erections greater than 6 hours) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Carcinogenicity

VIAGRA shows no evidence of any mutagenic or carcinogenic potential.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers although there are no data in patients with erectile dysfunction.

Use in Pregnancy and Lactation

VIAGRA is not indicated for use by women.

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. The dose results in total systemic drug exposure (AUC) for unbound sildenafil and its major metabolite of greater than 60 times the exposure observed in human males given the maximum recommended human dose (MRHD) of 100 mg. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In non-pregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well controlled studies of sildenafil in pregnant women.

VIAGRA is not indicated for use in nursing mothers. No information is available on its secretion into breast milk.

Effect on ability to drive and use machines

As transient visual disturbances and dizziness have been reported in some patients taking VIAGRA, particularly at the 100 mg dose, patients should be aware of how they react to VIAGRA before driving or operating machinery, and the doctor should advise accordingly.

Adverse Reactions

Clinical trial data

VIAGRA was administered to over 3700 patients (aged 19-87) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

Treatment with VIAGRA was well tolerated. In placebo controlled clinical studies, the discontinuation rate due to adverse events was low and similar to placebo. The adverse events were generally transient and mild to moderate in nature.

Across trials of all designs, the profile of adverse events reported by patients receiving VIAGRA was similar. In fixed dose studies, the incidence of adverse events increased with dose. The nature of the adverse events in flexible dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed dose studies.

When VIAGRA was taken as recommended (on an as needed basis in flexible dose placebo controlled clinical trials) the following adverse events were reported:

Table 1.

Adverse Events Reported by ≥ 2% of Patients Treated with VIAGRA or Placebo in PRN Flexible Dose Phaseii/III Studies.

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA (N=734)	PLACEBO (N=725)
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision+	3%	0%
Diarrhoea	3%	1%

Dizziness	2%	1%
Rash	2%	1%

+Abnormal Vision: Mild and transient predominantly colour tinge to vision, but also increased perception to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision. This effect was more common at doses of 100 mg or more.

Other adverse reactions occurred at a rate of >2%, but equally commonly on placebo: respiratory tract infection, back pain, flu syndrome and arthralgia.

In fixed dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses.

At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

No cases of priapism were reported during controlled clinical trials.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a whole: infection, face oedema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischaemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy, vasodilation.

Digestive: nausea, vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, oesophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal haemorrhage, gingivitis.

Haemic and Lymphatic: anaemia and leukopenia.

Metabolic and Nutritional: thirst, oedema, gout, unstable diabetes, hyperglycaemia, peripheral oedema, hyperuricemia, hypoglycaemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypaesthesia.

Respiratory: rhinitis, respiratory disorder, asthma, dyspnoea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special senses: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye haemorrhage, cataract, dry eyes.

Urogenital: prostatic disorder, cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital oedema and anorgasmia.

Post marketing data

Cardiovascular: serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack and hypertension, have been reported post marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors. Tachycardia, hypotension, syncope, and epistaxis have also been reported post marketing. Rare spontaneous reports have been received of hypotensive events after the use of sildenafil in combination with alpha blockers.

Other events

Other events reported post marketing to have been observed in temporal association with VIAGRA and not listed in the clinical trials adverse reactions section include:

Nervous: seizure, seizure recurrence and anxiety

Urogenital: priapism, haematuria and prolonged erection

Ocular: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular oedema.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (See Contraindications and Warnings and Precautions).

Body as a whole: hypersensitivity reaction.

Interactions

Effect of other drugs on VIAGRA.

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 and inducers of these isoenzymes may increase sildenafil clearance.

In-vivo studies:

Cimetidine (800 mg), a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with VIAGRA (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).

Coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with Viagra (100 mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC. (see **Dosage And Administration**). Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have still greater effects.

Coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. (see **Dosage And Administration**).

Since systemic exposure to sildenafil increases on co-administration with inhibitors of CYP3A4, the VIAGRA dose may have to be reduced depending on tolerability.

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

There is no information on the interaction between sildenafil and cyclosporine.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampicin, will decrease

plasma levels of sildenafil.

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). However, there was no increased incidence of adverse events in these patients.

Population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors, CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, ACE inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as barbiturates).

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, Cmax, Tmax, elimination rate constant or subsequent half-life of sildenafil or it's major circulating metabolite.

Effects of VIAGRA on other drugs

In-vitro studies

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} > 150 µM). Given sildenafil peak plasma concentration of approximately 1 µM 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:

In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

No significant interactions were shown when sildenafil 50 mg was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates. [see **Effects of other drugs on Viagra** for details of the effects of saquinavir and ritonavir on the pharmacokinetics of sildenafil].

Sildenafil causes a small reduction in supine and tilted diastolic blood pressure (3.5 and 6.1mmHg respectively) in healthy subjects who had a blood alcohol level of 80 mg/dL.

No interaction was seen when VIAGRA (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additive reduction on supine blood pressure (systolic, 8 mmHg; diastolic 7 mmHg) was of a similar magnitude to that seen when VIAGRA was administered alone to healthy volunteers (see **Actions**).

Analysis of the safety database showed no difference in the side effect profile in patients taking VIAGRA with and without anti-hypertensive medication.

VIAGRA was shown to potentiate the hypotensive effect of acute and chronic nitrates. **Therefore, use of nitric oxide donors, organic nitrates or organic nitrites in any form, either regularly or intermittently, with VIAGRA is contraindicated** (see **Contraindications**).

Overdosage

Overdose information is limited. In studies with healthy volunteers, of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates and severities were increased. Survival is reported in a 42-year-old female following an overdose with 2,000 mg sildenafil. In cases of overdose, standard supportive measures should be adopted as required. Sildenafil blood levels are not clinically useful. Monitor ECG and blood pressure in symptomatic patients. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma protein and not eliminated in the urine.

Contact the Poisons Information Centre for advice on the management of an overdose.

Pharmaceutical Precautions

Shelf life: 60 months. Store below 30°C.

Medical Classification

Prescription medicine.

Package Quantities

VIAGRA tablets (25 mg, 50 mg & 100 mg) are presented in blister packs of 4 tablets.

Name and Address

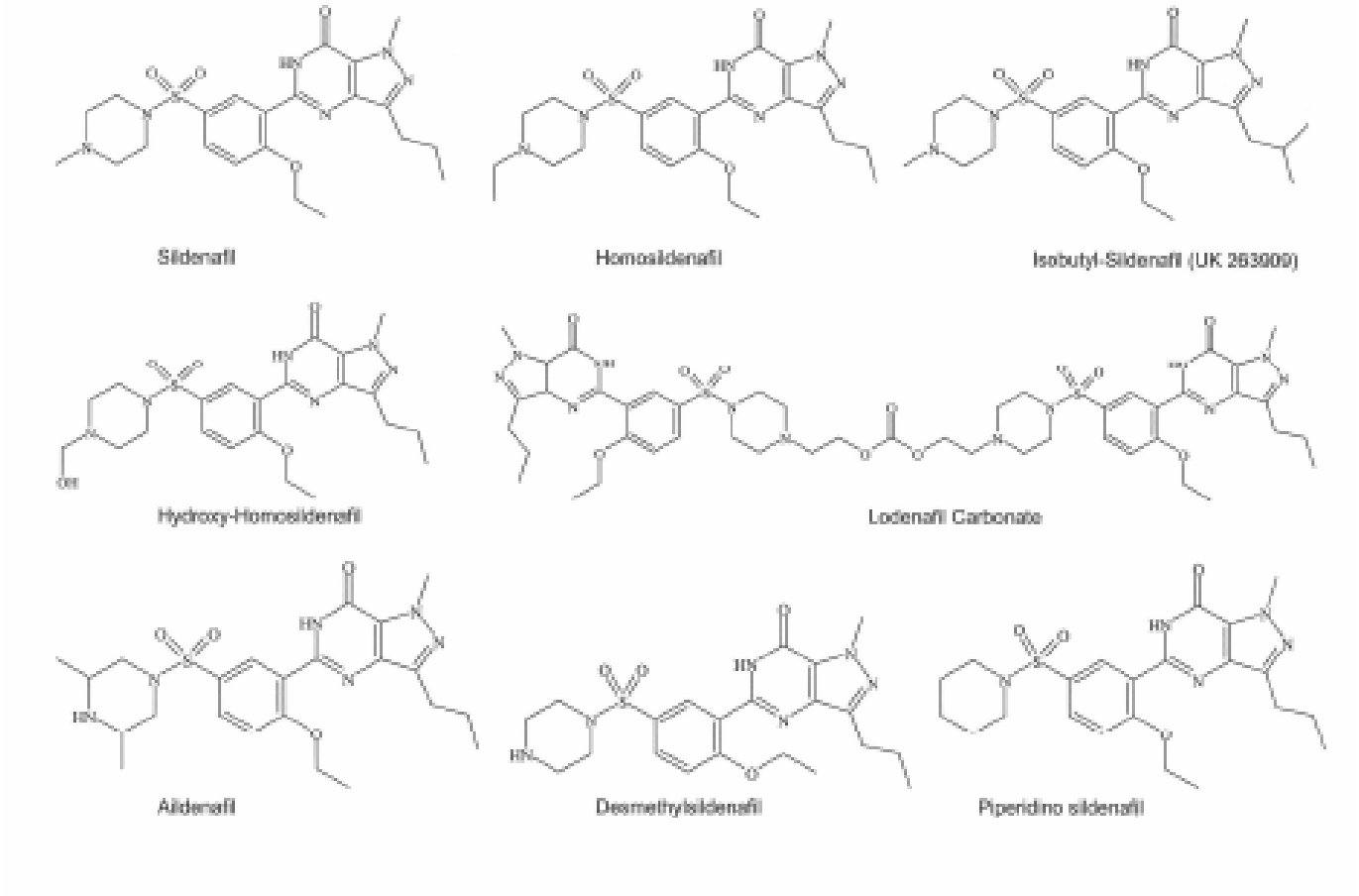
Pfizer New Zealand Ltd
PO Box 3998
Auckland, New Zealand

Toll Free: 0800 736 363

Date of Preparation

22 January 2008.

ANNEX 2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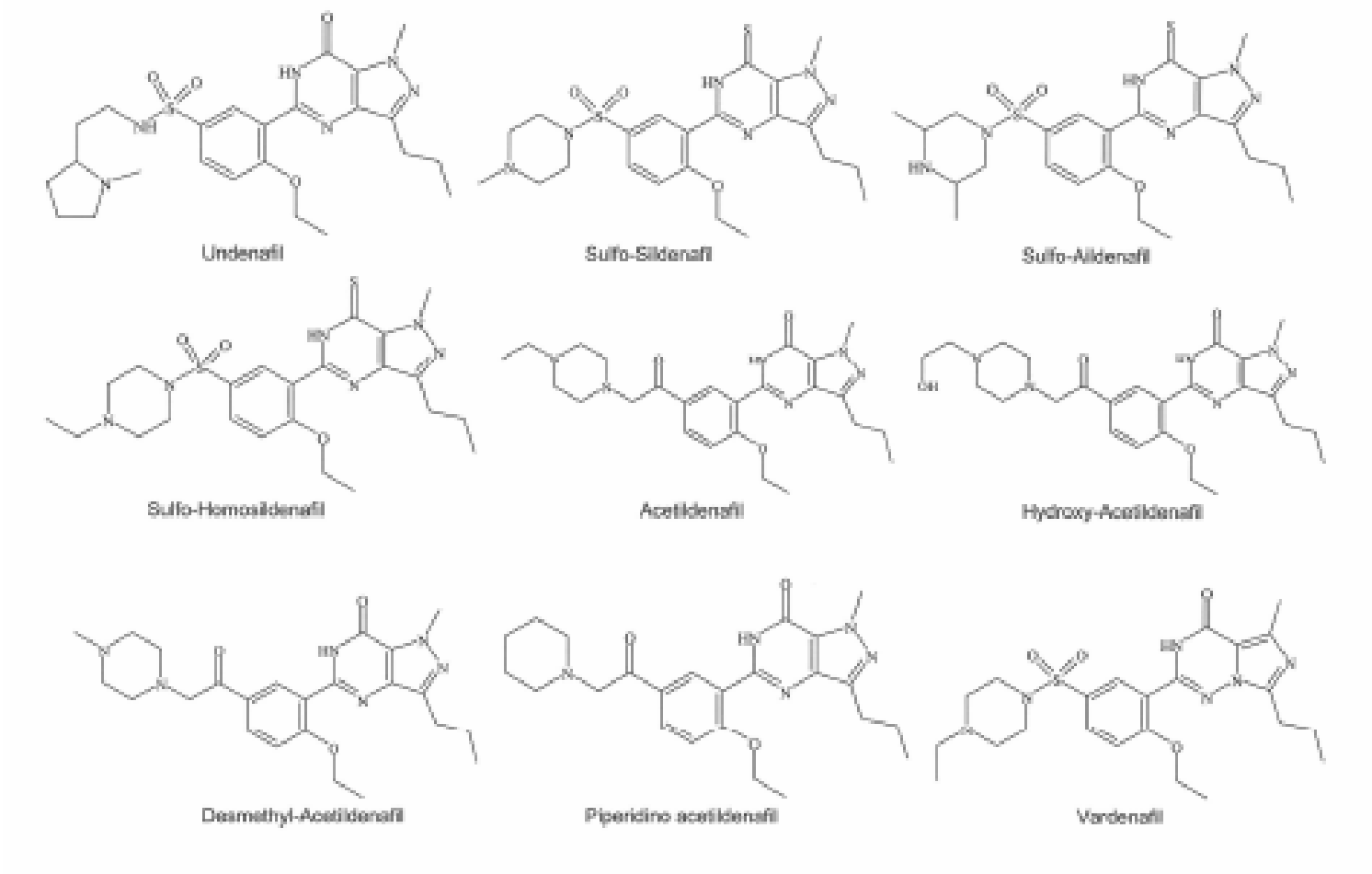
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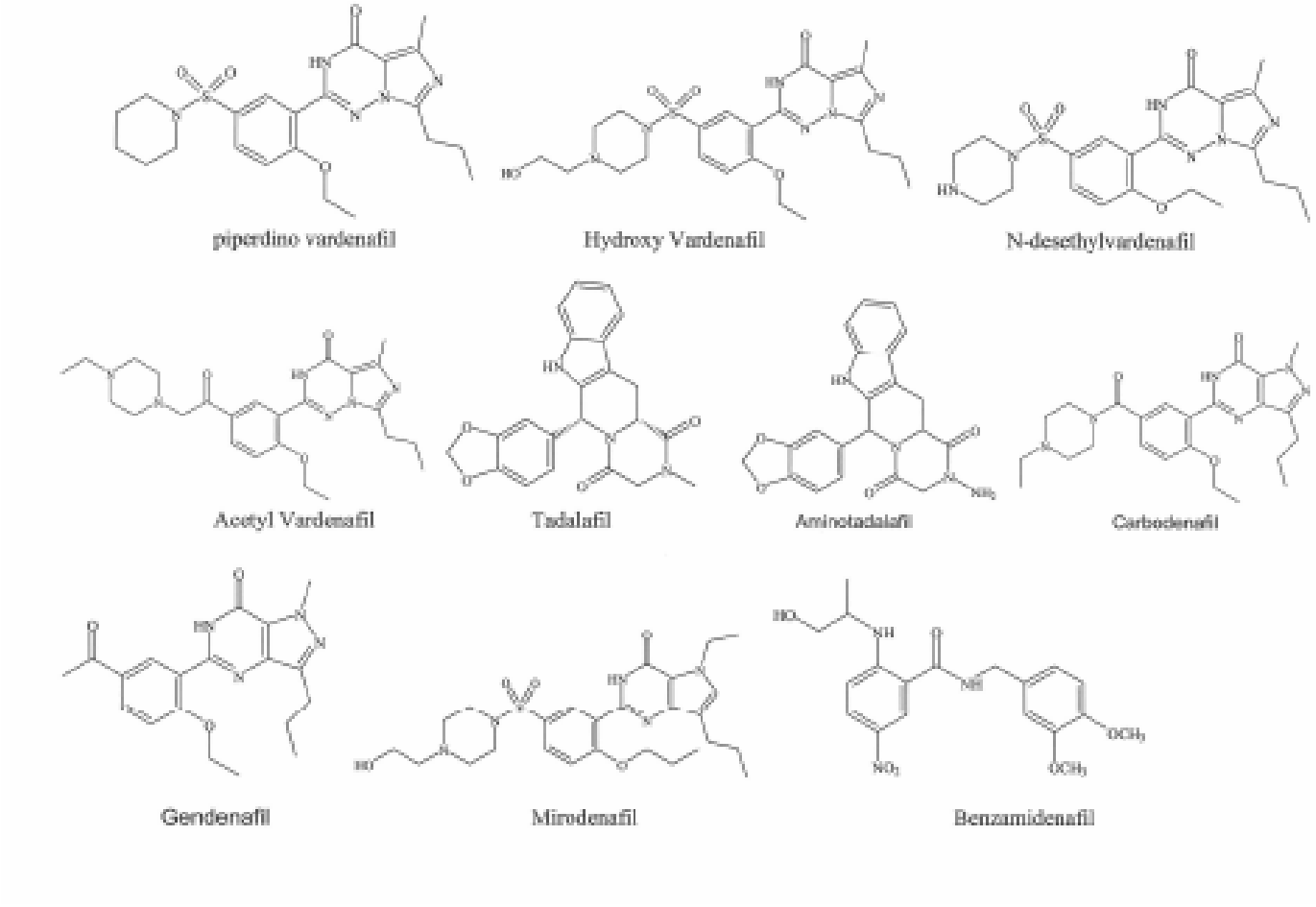
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Carbodenafil
Gendenafil
Mirodenafil
Benzamidenafil

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY

HOT TOPICS

- Media Releases
- Alerts/Letters
- Recall Notices
- Herbal, Traditional and Complementary Medicines
- Papers/Reports
- Trans-Tasman Agency Project News
  - Consultations
  - Newsletters
- Medsafe News
- Oral Contraceptives/HRT
- Industrial Hemp
- MeNZB

Media Releases

Health warning - Erectile dysfunction / sexual enhancement 'herbal' products

8 August 2008

Health warning issued under Section 98 of the Medicines Act 1981

Director-General of Health, Stephen McKernan, is warning people about the potential health dangers associated with three products promoted and sold in New Zealand for sexual enhancement or the treatment of erectile dysfunction which may contain an undeclared therapeutic substance.

This statement about the three products is being issued by the Director-General under Section 98 of the Medicines Act 1981, following investigations by the Ministry of Health's medicines safety arm, Medsafe.

The products are Rize 2 the Occasion (also known as Rize 2), Rose 4 Her and Viapro. The products appear to have been sold by retail from 'adult' shops and over the internet.

The United States FDA has issued a warning that products on the US market with these names had been tested and recalled after they were found to contain the substance thiomethisosildenafil which is an analogue of sildenafil. Thiomethisosildenafil is expected to have similar therapeutic actions and adverse effects as sildenafil the active ingredient of the prescription medicine Viagra. Sildenafil is known to interfere with some heart medications and its use could be fatal to some individuals.

"Consumers should immediately stop taking Rize 2 the Occasion, Rose 4 Her and Viapro and seek medical advice from their doctor if they are taking other medicines or if they have felt unwell when taking any of these products," said Mr McKernan.

Stephen McKernan also warned that Medsafe has previously identified a number of other products being sold in shops and over the internet to treat erectile dysfunction or for sexual enhancement that have also been adulterated with prescription medicines. Consumers should treat erectile dysfunction products offered for sale without a prescription with caution and seek medical advice before using them.

Under the medicines legislation, sponsors, distributors and importers are responsible for the products they sell and must be aware of all the active ingredients they contain and seek approval prior to selling them if required by the legislation.

ENDS

For further information please contact:
Michael Flyger, Media Advisor, Ministry of Health ph 04 496 2265 or 027 474 6878

Summary of Regulatory Action for ED Analogues in 2008 (1 January 2008 to 19 September 2008) ANNEX 4

Country (Regulator)	Date of public advisory	Product Name	Analogue detected	Action taken	Link to alert, warning or advisory
Australia (TGA)					No alerts, warnings or advisory statements issued to date.
Canada (Health Canada)	6/8/08	Rize 2 The Occasion	Thiomethisosildenafil	Warning issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_124-eng.php
	10/3/08	ADAM	Sildenafil analogue	Warning issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_39-eng.php
	11/8/08	Xiadafil VIP	Hydroxyhomosildenafil	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_130-eng.php
	11/8/08	Oyster Extract	Sildenafil analogue	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_129-eng.php#more
	11/8/08	China Vigour	Nor-acetildenafil	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_128-eng.php
	11/8/08	Virility Power	Hydroxyhomosildenafil	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_119-eng.php
	7/7/08	Shangai Regular (also known as Shangai Chaojimengnan), Actra-Sx, An unknown product containing the plant Lycium barbarum L., Adam Free, NaturalUp, Erextra,	Sildenafil or sildenafil analogue	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_106-eng.php

		Yilishen, Blue Steel, Hero, Naturalë Super Plus			
	29/4/08	Tian Li	Hydroxyhomosildenafil	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_65-eng.php
	17/4/08	Aspire 36 and Aspire Lite	Sildenafil analogues	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_58-eng.php
	18/8/08	Armstrong Natural Herbal Supplement, Enhanix New Extra Men's Formula, Power 58 Extra, and Platinum Power 58 Extra	Tadalafil or tadalafil or vardenafil analogues	Foreign product alert issued	http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2008/2008_136-eng.php
Europe (EMEA)					No alerts, warnings or advisory statements issued to date.
UK (MHRA)	30/4/08	China Vigour Blue Steel or Hero	Nor-acetildenafil Sildenafil analogues	Warning issued to consumers	http://www.mhra.gov.uk/CON014975
USA (FDA)	31/7/08	Viapro	Thiomethisosildenfil	Advisory to consumers and healthcare professionals	http://www.fda.gov/medwatch/safety/2008/safety08.htm#Viapro
	25/3/08	Blue steel Hero	Sildenafil analogue	Warning issued to consumers	http://www.fda.gov/bbs/topics/NEWS/2008/NEW01809.html
	28/7/08	Rize 2 The Occasion	Thiomethisosildenfil	Recall - Firm Press	http://www.fda.gov/oc/po/firmrecalls/jackdistribution07

		Rose 4 Her		Release	_08.html
	29/5/08	Viril-ity Power Capsules (VIP)	Hydroxyhomosildenafil	Recall - Firm Press Release	http://www.fda.gov/oc/po/firmrecalls/internationalpharma05_08.html
Hong Kong (Department of Health)	25/7/08	Dr Life	Aminotadalafil	Public advisory	http://www.dh.gov.hk/english/press/2008/080725-3.html
	18/6/08	Onyo	Acetildenafil and pseudovardenafil	Public advisory	http://www.dh.gov.hk/english/press/2008/080618-2.html
	7/5/08	Oyster extract	Hydroxyacetildenafil	Public advisory	http://www.dh.gov.hk/english/press/2008/080507-6.html
	16/6/08	Sweet Energizer Vitality Candy	Aminotadalafil	Public advisory	http://www.dh.gov.hk/english/press/2008/080616-7.html
Singapore (HSA)					No alerts, warnings or advisory statements issued to date.
Switzerland (Swissmedic)	13/8/08	PowerTabs	Sildenafil analogue	Warning issued	http://www.swissmedic.ch/cgi/news/index.asp?sitetype=laien&news_id=5340