European Medicines Agency
*Post Authorisation Evaluation of Medicines for Human Use*

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# WITHDRAWAL ASSESSMENT REPORT FOR VIAGRA

International Nonproprietary Name:
**Sildenafil citrate**

**Procedure No. EMEA/H/C/0202/II/0045**

Day 120 Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase (SGPT) |
| AST | Aspartate Aminotransferase (SGOT) |
| BUN | Blood Urea Nitrogen |
| CAD | Coronary Artery Disease |
| cGMP | Cyclic Guanosine Monophosphate |
| CHMP | Committee for Proprietary Medicinal Products for Human Use |
| CI | Confidence Interval |
| ECG | Electrocardiogram |
| ED | Erectile dysfunction |
| EMEA | European Medicines Evaluation Agency |
| EU | European Union |
| GTN | Glyceryl Trinitrate |
| MA | Marketing authorisation |
| MAA | Marketing authorisation application |
| MAH | Marketing Authorisation Holder |
| MED | Male erectile dysfunction |
| mg | Milligram |
| NAION | Non-arteritic ischaemic optic neuropathy |
| NO | Nitric Oxide |
| PDE-5 | Phosphodiesterase 5 |
| PSUR | Periodic Safety Update report |
| PT | Preferred term |
| RMP | Risk Management Plan |
| SAE | Serious adverse event |
| SPC | Summary of Product Characteristics |
| ULN | Upper Limit of Normal |

# I. RECOMMENDATION

Based on the review of the data and the MAH's responses to the Request for Supplementary Information (EMEA/CHMP/11919/2008) on safety and efficacy, the CHMP considers that the changing of the classification of Viagra 50 mg, in the treatment of male erectile dysfunction (MED), from 'medicinal product subject to medical prescription' to 'medicinal product **not** subject to medical prescription' is **not approvable** since major objections remain identified which preclude a recommendation for changing the classification of Viagra 50 mg at present time.

The major objections precluding a recommendation for changing the classification of Viagra 50 mg, pertain mainly to the following principal deficiencies: the ability of the patient to self diagnose the underlying conditions (possibly resulting in delay in diagnosis and treatment), and correctly assess the warnings and the contra-indications, the need for medical advice to be given to patients who require a treatment initiation with a lower dose and the effect of the change of the classification on the magnitude of the incorrect use (particularly in young patients).

# II. EXECUTIVE SUMMARY

## II.1 Problem statement

Male erectile dysfunction (MED) is the persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance[1]. Worldwide, MED is estimated to affect more that 150 million men[2], and that number is expected to exceed 300 million men by the year 2025[3] . The overall prevalence of self-reported MED in the male population has been estimated at 19% [4]. This prevalence is known to increase in patients sharing associated risk factors.[5]

About 80% of cases of MED are believed to have an organic cause, other cases being psychogenic (or mixed psychogenic and organic) in origin.

Most cases of MED are believed to be multifactorial and secondary to disease, stress, trauma (such as spinal cord injury, pelvic and prostate surgery), or drug adverse effects that interfere with the coordinated psychological, neurological, endocrine, vascular and muscular factors necessary for normal erections[6].

Risk factors include increasing age, smoking, sedentary lifestyle, and obesity. The prevalence of MED also increases in people with diabetes mellitus, hypertension, heart disease, anxiety, and depression. Age is a key risk factor for MED.

Complete MED has an estimated prevalence of about 5% in men aged 40 years increasing to 15% at age 70 years.

On 14 September 1998, Viagra (sildenafil) 25 mg, 50 mg and 100 mg film coated tablets were authorised in the European Union (EU) in the following indication:

[1] National Institutes of Health (NIH) Consensus Conference, 1993
[2] NIH Consensus Conference, 1993
[3] Aytac, 1999
[4] Shabsigh, 2005
[5] (Shabsigh, 2003).
[6] AACE Male Sexual Dysfunction Task Force, 2003

*'Treatment of men with 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.'*

For the treatment of MED, the recommended dose of sildenafil is 50 mg taken about one hour before sexual activity with a dose range of 25-100 mg.

In this type II variation application, the MAH applied to change the classification of Viagra 50mg from 'medicinal product subject to prescription' to 'medicinal product **not** subject to prescription'.

According to article 71 of Directive 2001/83/EC, as amended and the European Commission Guideline on *'Changing the Classification for the Supply of a Medicinal Product for Human Use"* (January 2006), the MAH considered that sildenafil 50 mg no longer meets the criteria for classifying the product as subject to medical prescription, and therefore proposed to change its classification to **not** subject to medical prescription.

### II.2 About the product

Viagra (sildenafil) is a potent inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa (a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response.

## III. SCIENTIFIC OVERVIEW AND DISCUSSION

### III.1 Quality aspects

Not applicable

### III.2 Non clinical aspects

There are no new non clinical data presented in this application. However, the toxicity profile (including general and reproductive toxicities, genotoxic and carcinogenic properties) are discussed in the scope of the change in the classification of Viagra 50 mg to **not** subject to medical prescription.

**Toxicology**

Sildenafil is known to have low general toxicity and no relevant reproductive toxicity, genotoxicity or carcinogenic properties.

In the original marketing authorisation application (MAA) dossier, toxicokinetic data for both sildenafil and for the main metabolite (UK-103,320) indicated a large margin between plasma exposure to drug-related components in man and that associated with toxicity in the rat and dog.

Non-clinical studies showed that there were no adverse effects on the fertility of either sex, and no evidence of maternal, embryo- or foetal- toxicity, or teratogenic potential.

Sildenafil did not induce mutations in bacterial or mammalian cells in vitro, and did not cause clastogenic activity in vivo or in vitro.

There was no evidence of a carcinogenic effect in mice or rats, indicating that sildenafil had no carcinogenic potential in man.

## III.3 Clinical aspects

### III.3.1 Clinical Pharmacology

There are no new clinical pharmacology data presented in this application. However, the potential interactions with commonly used medicines are discussed in the scope of the change in the classification of Viagra 50 mg to not subject to medical prescription.

Sildenafil has a low interaction potential towards other drugs. As sildenafil is metabolised primarily by CYP3A4, increased sildenafil plasma concentrations are observed in case of concomitant treatment with CYP3A4 inhibitors and a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors.

In addition, increased sildenafil plasma concentrations are observed in elderly, patients with severe renal insufficiency and patients with hepatic insufficiency. Treatment initiation at a lower dose should be considered only for patients with severe renal insufficiency and patients with mild to moderate hepatic insufficiency, while patients with severe hepatic insufficiency are contraindicated. Despite the increased plasma concentrations, no dose adjustment is advised for the elderly patients. As co-administration with alpha-blockers may result in hypotension, initiation of sildenafil at a dose of 25 mg should also be considered.

### III. 3.2 Clinical efficacy

Doses of 25 mg, 50 mg, or 100 mg sildenafil taken approximately an hour before sexual activity produced both statistically and clinically significant improvement in the ability to achieve and maintain erections sufficient for sexual intercourse.

The effectiveness of sildenafil increased with dose up to 100 mg, but there was no improvement in efficacy with increasing the dose to 200 mg.

At the time of the first renewal of the marketing authorisation (MA), approximately 200 additional independent clinical studies or case series with clinical data on over 12,000 patients had been reported. These studies generally produced efficacy findings consistent with those reported from the pivotal and other trials supportive of the initial marketing authorisation application[7].

Viagra was renewed in 2003 with a 5 year PSUR cycle. The second renewal is currently being evaluated by the CHMP and an opinion is expected during this June CHMP meeting.

Overall, since the initial granting of the MA, the therapeutic effect of Viagra in the approved indication remains unchanged.

### III.3.3 Clinical safety

#### Cumulative experience

Since the last renewal, no PSUR were submitted according to the PSUR cycle agreed by CHMP in 2003.

[7] e.g. Jarow, 1999; Guay, 2001; Ng, 2002; Palumbo, 2001; McMahon, 2000).

Within this application, the safety profile of sildenafil was thus evaluated from a comprehensive 67 MED placebo controlled double blind studies dataset (data lock point: 1 June 2007) and from post-marketing experience (i.e. spontaneously reported cases from health professionals, non-healthcare professionals, health authorities, or the medical literature, data lock point: 15 July 2007).

Overall, common adverse events (AEs) experienced by sildenafil patients in both MED placebo controlled double blind studies and post-marketing surveillance were those related to the pharmacology of PDE-5 inhibition such as headache, flushing and dyspepsia. Other frequently reported events are dizziness, altered vision, nasal congestion, chromatopsia and palpitations. (See Table 1)

**Table 1**

**Table 18. Summary of AEs Reported in ≥ 2% of Sildenafil Cases (Any Sildenafil Group) Stratified by Known First Total Daily Dose Range Received in the MAH's Safety Database**

| MedDRA SOC/ Preferred Term (version 10.0) | First Total Daily Dose Range | | | | |
|---|---|---|---|---|---|
| | >0 and < 25 mg N=2,335 | > 25 mg and < 50 mg N=12,843 | > 50 mg and < 100 mg N=5,066 | > 100 mg N=255 | All Sildenafil N=39,277 |
| **Cardiac disorders** | | | | | |
| Acute myocardial infarction | 19 (0.8%) | 92 (0.7%) | 28 (0.6%) | 6 (2.4%) | 290 (0.7%) |
| Myocardial infarction | 43 (1.8%) | 273 (2.1%) | 95 (1.9%) | 11 (4.3%) | 987 (2.5%) |
| Palpitation | 43 (1.8%) | 236 (1.8%) | 48 (0.9%) | 6 (2.4%) | 526 (1.3%) |
| Tachycardia | 43 (1.8%) | 165 (1.3%) | 36 (0.7%) | 6 (2.4%) | 381 (1.0%) |
| **Eye disorders** | | | | | |
| Cyanopsia | 28 (1.2%) | 233 (1.8%) | 189 (3.7%) | 4 (1.6%) | 736 (1.9%) |
| Vision blurred | 52 (2.2%) | 244(1.9%) | 89 (1.8%) | 4 (1.6%) | 733 (1.9%) |
| Visual disturbance | 34 (1.5%) | 149 (1.2%) | 74 (1.5%) | 5 (2.0%) | 488 (1.2%) |
| **Gastrointestinal disorders** | | | | | |
| Dyspepsia | 72 (3.1%) | 415 (3.2%) | 174 (3.4%) | 2 (0.8%) | 1027 (2.6%) |
| Nausea | 56 (2.4%) | 276 (2.2%) | 82 (1.6%) | 5 (2.0%) | 606 (1.5%) |
| **General disorders and administration site conditions** | | | | | |
| Chest pain | 43 (1.8%) | 220 (1.7%) | 59 (1.2%) | 5 (2.0%) | 702 (1.8%) |
| Death | 12 (0.5%) | 89 (0.7%) | 28 (0.6%) | 7 (2.8%) | 531 (1.4%) |
| Drug effect decreased | 142 (6.1%) | 1090 (8.5%) | 397 (7.8%) | 5 (2.0%) | 2311 (5.9%) |
| Drug ineffective | 708 (30.3%) | 3803 (29.6%) | 2038 (40.2%) | 70 (27.5%) | 12,571 (32.0%) |
| Drug interaction | 62 (6.7%) | 248 (1.9%) | 121 (2.4%) | 11 (4.3%) | 932 (2.4%) |
| Feeling hot | 48 (2.1%) | 202 (1.6%) | 47 (0.9%) | 3 (1.2%) | 470 (1.2%) |
| Malaise | 26 (1.1%) | 130 (1.0%) | 40 (0.8%) | 6 (2.4%) | 392 (1.0%) |
| **Injury, poisoning and procedural complications** | | | | | |
| Accidental overdose | 1 (0.0%) | 5 (0.0%) | 6 (0.1%) | 13 (5.1%) | 40 (0.1%) |
| Drug administration error | 19 (0.8%) | 37 (0.3%) | 36 (0.7%) | 23 (9.0%) | 224 (0.6%) |
| Intentional drug misuse | 26 (1.1%) | 85 (0.7%) | 66 (1.3%) | 12 (4.7%) | 535 (1.4%) |
| Intentional overdose | 27 (1.2%) | 153 (1.2%) | 121 (2.4%) | 153 (60%) | 583 (1.5%) |
| Overdose | 28 (1.2%) | 154 (1.2%) | 65 (1.3%) | 42 (16.5%) | 392 (1.0%) |
| **Nervous system disorders** | | | | | |
| Dizziness | 97 (4.2%) | 502 (3.9%) | 167 (3.3%) | 14 (5.5%) | 1235 (3.1%) |
| Headache | 320 (13.7%) | 1929 (15.0%) | 574 (11.3%) | 20 (7.8%) | 4586 (11.7%) |
| Tremor | 9 (0.4%) | 49 (0.4%) | 15 (0.3%) | 6 (2.4%) | 118 (0.3%) |
| **Psychiatric disorders** | | | | | |
| Suicide attempt | - | 3 (0.0%) | 3 (0.1%) | 8 (3.1%) | 27 (0.1%) |
| **Reproductive system and breast disorders** | | | | | |
| Erectile dysfunction | 164 (7.2%) | 1132 (8.8%) | 449 (8.9%) | 10 (3.9%) | 2762 (7.0%) |
| Erection increased | 32 (1.4%) | 201 (1.6%) | 80 (1.6%) | 17 (6.7%) | 736 (1.9%) |
| Priapism | 17 (0.7%) | 104 (0.8%) | 52 (1.0%) | 18 (7.1%) | 389 (1.0%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | | |
| Dyspnoea | 29 (1.2%) | 163 (1.3%) | 54 (1.1%) | 6 (2.4%) | 409 (1.0%) |
| Nasal congestion | 102 (4.4%) | 530 (4.1%) | 156 (3.1%) | 5 (2.0%) | 1157 (2.9%) |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Erythema | 78 (3.3%) | 304 (2.4%) | 59 (1.2%) | 3 (1.2%) | 690 (1.8%) |
| **Vascular disorders** | | | | | |
| Flushing | 255 (10.9%) | 1367 (10.6%) | 409 (8.1%) | 14 (5.5%) | 3129 (8.0%) |
| Hot flush | 51 (2.25) | 183 (1.4%) | 26 (0.5%) | 1 (0.4%) | 360 (0.9%) |

*Source: SCS Tables 1.6.2, 1.6.2.1, 1.6.2.2, 1.6.2.3 and 1.6.2.4*

Overall, the safety profile of Viagra in the approved indication and respecting the restrictions mentioned in the SPC remains favourable.

However, there were two safety issues concerning PDE5 inhibitors since the last renewal i.e NAION and sudden deafness risks for which the CHMP recommended class labelling.

At its April 2006 Plenary meeting, the CHMP recommended to contraindicate the use of any PDE5 inhibitors in those patients having had a NAION in one eye, either in connection or not with a previous PDE5 inhibitor exposure. Subsequently a type II variation was approved to include a sildenafil contraindication for patients with a prior episode of NAION (EMEA/H/C/202/II/26).

At its December 2007 meeting, the CHMP recommended to include sudden deafness as an adverse drug reaction for all PDE5 inhibitors. Subsequently, a type II variation was approved by the CHMP (EMEA/H/C/202/II/51).

- *Additional safety reviews*

In the scope of this application, special populations (patients with renal or hepatic impairment), safety drug-drug interactions and other interactions were reviewed as specific safety considerations.

**Safety in special populations**

**1) Patients with renal impairment**

Renal clearance of sildenafil is low, accounting for less than 2% of an administered dose.

Study 148-214 conducted in renal impaired patients and previously submitted as part of the MAA, showed that the pharmacokinetics of sildenafil and its primary metabolite (UK-103,320) were significantly altered in patients with severe renal impairment (creatinine clearance <30 mL/min).

A total of 21 patients were identified from the 67 MED placebo controlled, double blind dataset as having a moderate degree of renal impairment at baseline (defined as any patient who had a laboratory value of >1.5 x ULN blood urea nitrogen (BUN)/Urea and >1.5 x ULN Creatinine at baseline).

Of these 21 patients, 7 patients were randomised to sildenafil and 14 were randomised to placebo. Of those patients with laboratory parameter data available either throughout the study or at the end of the study, no sildenafil or placebo patients showed worsening of their BUN/urea or creatinine values.

Of the 21 patients identified with moderate renal impairment, only 2/7 (29%) sildenafil patients [abdominal pain and sciatica (1), mild event of peripheral oedema (1)] and 9/14 (64%) placebo patients experienced AEs.

No analysis of the post-marketing data has been conducted concerning impaired renal patient population.

Considering the above, the CHMP is of opinion that the involvement of a physician to establish the need for treatment initiation with a lower dose in patients with severe renal insufficiency, is necessary.

**2) Patients with hepatic impairment**

Sildenafil is extensively and rapidly metabolised by the liver, primarily by CYP3A4 enzymes.

Study 148-221 conducted in hepatic impaired patients and previously submitted as part of the MAA, showed that the pharmacokinetics of sildenafil and its primary metabolite (UK-103,320) were significantly altered in patients with chronic stable cirrhosis, which suggested a reduction in first-pass metabolism as well as systemic clearance.

A total of 45 patients were identified from the 67 MED placebo controlled, double blind dataset as having a moderate degree of hepatic impairment at baseline using the laboratory criteria (defined as any patient from MED placebo controlled, double blind studies who had a laboratory value of 1.5 x ULN AST/ALT and/or >1.5 x ULN Alkaline phosphatase and/or >1.5 ULN Total Bilirubin. Two of the three criteria had to be elevated to be identified as having moderate hepatic impairment).

Of these 45 patients, 26 patients were randomised to sildenafil and 19 were randomised to placebo.

Of those patients with laboratory parameter data available either throughout the study or at the end of the study, 6 sildenafil and 0 placebo patients showed worsening (≥2 fold their baseline value) of their AST/ALT or alkaline phosphatase or total bilirubin values during at least one visit during the study.

Of the 45 patients identified with moderate hepatic impairment, 20/26 (77%) sildenafil patients 7/19 (37%) placebo patients experienced AEs.

AEs that were reported in more than one sildenafil patient with moderate hepatic impairment included: dyspepsia (2), upper respiratory tract infection (2), alanine aminotransferase increased (3), aspartate aminotranferase (3), dizziness (2), headache (2) and flushing (3).

AEs that were attributed to study drug (sildenafil) by the Investigator included dyspepsia, dizziness, flushing, headache, myalgia, ejaculation failure and optic nerve cup/disc ratio (investigator term: asymmetric cup/disc ratio), all of which were mild in severity.

Considering the above, the CHMP is of opinion that the involvement of a physician to establish the need for treatment initiation with a lower dose in patients with hepatic insufficiency, is necessary.

**Safety related to drug-drug interactions and other interactions**

**1) with nitrates**

Several clinical studies have investigated this interaction at different doses of sildenafil and with various nitrates, including glyceryl trinitrate (GTN), isosorbide mononitrate and nicorandil.

Changes in blood pressure with the 50 mg dose of sildenafil were investigated in clinical studies A1481065 and 148-231, previously submitted at the time of MAA.

In Study 148-231, doses of 0.5 mg sublingual GTN with either 50 mg sildenafil or placebo produced mean maximum changes in sitting systolic blood pressure of -36.0 mmHg in the sildenafil/GTN group and -25.9 mmHg in the placebo/GTN group – an effect which was statistically significant [p=0.0053; 95% confidence interval (CI) -16.5, -3.6].

In Study A1481065, lower doses of sublingual GTN (0.4 mg) were used with either 50 mg sildenafil or placebo, and produced lower mean maximum changes in sitting systolic blood pressure which approached statistical significance [p=0.0653; 95% confidence interval (CI) -7.96, +0.25].

Similar results were seen for sitting diastolic blood pressure in both studies. Hypotensive episodes were reported as adverse events by some patients in these interaction studies consistent with the pharmacodynamic data.

These previous studies indicated that there was potential for a clinically significant interaction at the 50 mg dose of sildenafil and above when used with doses of nitrates commonly used in clinical practice.

Given this clinically significant interaction (fatal cardiac risk), the CHMP considers this interaction as a direct danger.

**2) with CYP3A4 inhibitors**

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route).
From the Phase I CYP3A4 inhibitor interaction studies, the AE profile of sildenafil 50 mg and 100 mg across studies 148-002 and 148-234 was consistent with PDE-5 inhibition and similar in the absence or presence of CYP3A4 inhibitors.

A safety analysis across all MAA studies indicated that the overall frequency of all causality AEs was higher for sildenafil patients (76%) and placebo patients (53%) with concomitant CYP3A4 inhibitors than for those sildenafil (63%) and placebo (41%) alone.

Furthermore, the overall frequency of discontinuation due to AEs was comparable for sildenafil (2%) and placebo (3%) with concomitant CYP3A4 inhibitors and sildenafil (3%) and placebo (3%) patients without.

Subsequent to MAA approval, further sildenafil interaction studies with protease inhibitors, the majority of which are CYP3A4 inhibitors, were performed. Ritonavir increased sildenafil maximum plasma concentrations and exposure to a much greater effect than that observed when sildenafil was co-administered with steady-state saquinavir. However, in both studies, sildenafil was generally well tolerated, with no SAEs and no increased frequency of AEs or clinically significant changes in laboratory, ECG or vital signs.

In total, 67 sildenafil and 43 placebo patients were identified as having taken sildenafil and a concomitant CYP3A4 inhibitor in the 67 MED placebo controlled, double blind studies. Sildenafil doses ranged from 5-200 mg, with the 50 mg and 100 mg being the most common sildenafil doses in this subset. Erythromycin and cimetidine were the most common concomitant CYP3A4 inhibitors taken with sildenafil in this subset.

There were more AEs reported by sildenafil patients (165 in total) than placebo patients (53 in total) receiving concomitant CYP3A4 inhibitors, though on the whole the majority of events (107/165) were mild in severity for patients receiving sildenafil and CYP3A4 inhibitors . Fewer sildenafil patients experienced a severe AE (12/165) than placebo patients (10/53).

In general, the frequency of AEs in sildenafil and placebo patients taking CYP3A4 inhibitors was generally higher than that observed in the sildenafil and placebo groups in the MED clinical studies.
The most commonly reported all causality AEs in sildenafil patients with concomitant CYP3A4 inhibitor administration were dyspepsia, headache and flushing which are known adverse drug reactions with sildenafil treatment and the pharmacology of PDE-5 inhibition.

The frequency of dyspepsia, flushing, nausea, and nasopharyngitis were all higher for sildenafil treated patients taking CYP3A4 inhibitors than placebo patients taking CYP3A4 inhibitors.

Additionally, comparing the actual frequencies for these AEs between sildenafil and placebo groups with the CYP3A4 inhibitor or MED dataset, the magnitude of difference in the frequency for these events is the same between sildenafil and placebo patients.

The profile of all causality AEs was similar between sildenafil patients who received 50 mg or 100 mg sildenafil and who took a concomitant CYP3A4 inhibitor. Eye events such as visual disturbance and cyanopsia tended to occur at doses of 100 mg and 200 mg sildenafil, but this trend of increasing visual events with higher sildenafil doses has been observed previously in sildenafil clinical studies in the absence of CYP3A4 inhibitors.

Overall, visual events with sildenafil treatment were generally transient and resolved without intervention. The profile of treatment-related AEs was similar to all causality AEs.

Four SAEs were reported in the clinical MED dataset with concomitant CYP3A4 inhibitor use [subcutaneous abscess (1), reversible ischaemic neurological deficit (1), moderate atrial fibrillation (1), severe myocardial infarction (1)].

Nineteen cases identified from a total of 39,277 non-clinical study sildenafil cases received into the MAH's safety database through 15 July 2007.

The frequency of concomitant sildenafil and CYP3A4 use was lower in the post-marketing dataset (0.05%, 19/39277) than in the clinical MED studies (0.8%, 67/8691), though overall concomitant CYP3A4 and sildenafil use was relatively uncommon in both datasets. From these 19 cases, 78 AEs were identified.

Of the four cases (21%) that reported a fatal outcome, the cause of death for three cases was due to cardiovascular events, of which two cases were possibly caused by a drug interaction between sildenafil (≤25 mg daily) and two antiretroviral medications (ritonavir and saquinavir) in one case and, to an interaction between sildenafil (dose unknown) and erythromycin in the second case.

The third case reported a suspected drug interaction between sildenafil (≤25 mg daily) and nitrates and the concomitant administration of cimetidine together with other medications.

Of the remaining 15 cases, the majority (9/15) reported events related to a decrease of sildenafil effect coded as Drug effect decreased (4 cases) or Drug ineffective (5 cases). The sildenafil daily dose was reported as 25 mg for two cases, 50 mg for two additional cases, and the remaining three cases reported a dose of unknown.

Considering the above, the CHMP is of opinion that the involvement of a physician to establish the need for treatment initiation with a lower dose in patients using concomitantly CYP3A4 inhibitors, is necessary.

**3) with alpha-blockers**

From the clinical MED placebo controlled, double blind dataset, 4.2% (368/8691) sildenafil and 5.0% (329/6602) placebo patients were identified as having taken sildenafil and a concomitant alpha-blocker.

Sildenafil doses ranged from 5-200 mg, with 50 mg and 100 mg doses being the most common sildenafil doses in this subset. Terazosin and doxazosin were the most common concomitant alpha-blockers taken with sildenafil in this subset.

There were more AEs reported by sildenafil patients (351) than placebo patients (189) receiving concomitant alpha-blockers, most of the events (252/351) were mild in severity for patients receiving sildenafil and alpha-blockers.
Fewer sildenafil patients experienced a severe AE (13/351) than placebo patients (16/189).

In general, the frequency of the AEs in sildenafil and placebo patients taking alpha-blockers was generally higher than that observed in the sildenafil and placebo groups not taking alpha-blockers.

The most commonly reported all causality AEs in sildenafil patients with concomitant alpha-blockers administration were dyspepsia, headache and flushing, which are known adverse drug reactions with sildenafil treatment and consistent with the pharmacology of PDE-5 inhibition.
The incidence of AEs expected from an interaction between sildenafil and an alpha-blocker (decreased blood pressure, orthostatic hypotension) was very low among this subset, and there were no cases of hypotension.

AEs reported at greater frequency in sildenafil than placebo patients taking alpha-blockers included: diarrhoea, dry mouth, urinary tract infection, myalgia, pain in extremity, insomnia, and cough.

Similar differences in frequencies among these AEs were also observed between sildenafil and placebo patients for the overall MED population.

Overall, the profile of all causality AEs was comparable between patients who received 50 mg sildenafil and 100 mg who took concomitant alpha-blockers. Flushing, dyspepsia, and nasopharyngitis were reported at a greater frequency in patients who received 100 mg than in those who received 50 mg of sildenafil.

Overall, there were ten SAEs experienced by nine sildenafil patients [urinary retention (1), musculoskeletal chest pain (1), haematuria (1), rectal haemorrhage (1), unilateral deafness (1) , cerebrovascular accident (1) , reversible ischemic neurological deficit (1) , syncope (1), pericarditis and respiratory tract infection (1) who received concomitant alpha-blockers. Of these, only one was considered related to sildenafil treatment (i.e. cerebrovascular accident).

From post-marketing data, Dataset A (defined as non-clinical study sildenafil cases reporting alpha-blockers as co-suspect and/or concomitant medications) and B (defined as non-clinical study sildenafil cases that reported MedDRA preferred term (PT) of drug interaction in addition to co-suspect and/or concomitant alpha-blockers) represent a reporting ratio of 4.1% (1600/39277) and 0.3% (135/39277) respectively.

The two case sets were identified from a total of 39,277 non-clinical study sildenafil cases received into the database through 15 July 2007. The five most common alpha-blockers reported as either co-suspect or concomitant medications were doxazosin (498 cases), terazosin (474 cases), tamsulosin (370 cases), carvedilol (138 cases) and prazosin (60 cases).

The events among dataset A and B that were reported at a >2% reporting rate than those in the all sildenafil dataset were not unexpected.

Most of these events were either mild events (nausea, vomiting, asthenia, fatigue, malaise); events consistent with a sildenafil-alpha blocker drug interaction (blood pressure decreased, dizziness, loss of consciousness, syncope, hypotension, orthostatic hypotension); or events associated with disorders, including signs and symptoms, that are commonly treated with alpha-blockers (blood pressure increased, prostate examination abnormal, prostate cancer, urinary hesitation, urine flow decreased, benign prostatic hyperplasia, ejaculation failure).

Considering the above, the CHMP is of opinion that the involvement of a physician to establish the need for treatment initiation with a lower dose in patients using concomitantly alpha blockers, is necessary.

**Discussion on safety**

The cumulative experience has shown that the safety profile when used under medical supervision has remained favourable. The most frequently reported adverse events among sildenafil treated patients were the result of an exaggerated pharmacological effect such as headache, flushing and dyspepsia. Other frequently reported events are dizziness, altered vision, nasal congestion, chromatopsia and palpitations. There were no dose-related increases in the incidence of severe AEs, SAEs, discontinuations or dose reductions (all causality or treatment-related). The exception to this was a known increased incidence of transient visual events at sildenafil doses ≥ 100 mg.

However, the CHMP considered that recently potential safety signals (NAION, sudden deafness) were observed that needed to be further investigated. Subsequently, routine pharmacovigilance activities (e.g PSUR monitoring) were proposed by the MAH. However, these activities would be presently considered

insufficient by the CHMP. Yearly review of these ADRs would be recommended, under non prescription status.

With respect to the specific safety considerations (special populations, drug-drug interactions), the CHMP was of the opinion that high incidence of conditions listed as contraindications, precautions or warnings and the high rate of usage of interacting drugs in the population may increase the incidence and risk of misuse, under non prescription setting. Importantly, the CHMP considered the dosage adjustment required in certain populations and the contraindication with nitrates to be of major concern, in the absence of medical supervision.

To address these major concerns related to the increased risk of incorrect use, the MAH argued that the dosage adjustment could be clearly identified by risk minimisation measures i.e strengthening of the warnings and contraindications on the SPC, Labelling and Package Leaflet, patients and pharmacist educational materials.

Additionally, the MAH proposed a treatment algorithm to clearly define patients who are suitable or non suitable for Viagra 50 mg. This proposed algorithm aimed at ensuring that high cardiac risk patients are excluded from treatment with Viagra 50 mg thus preventing the risk associated with the use of nitrates (see section III.3.5).

However, as expressed in its initial major objections, the CHMP considers the prevention of the risk for incorrect use unlikely to be ensured by such proposed risk minimisation measures, emphasizing that medical supervision is required prior to initiation of treatment with Viagra 50 mg.
With respect to the ability of the patients to correctly assess the warnings and contra-indications, particularly patients using nitrates, the CHMP has major concern that given the amount of concerned medicinal products, it is to be expected that a complete list encompassing nitrates and nitric oxide donors will be multifold, resulting in an uncorrect assessment by the patient of this contra-indication.

The initial major objection concerning the increased risk of incorrect use of Viagra 50mg remains to be addressed as well as the 'direct danger' associated with the use of nitrates.

### III.3.4 Overall benefit risk assessment

On the basis of data provided in this application, the CHMP considers that no new preclinical or clinical data are available which change the overall benefit-risk balance of Viagra, under the current conditions of use (see also EMEA/H/C/202/R52).

### III.3.5 Risk Management plan (RMP)

At the initial submission of this application, the MAH presented data on the potential for overdose, misuse and abuse.

**Overdose**

Out of 39,203 sildenafil case reports (including spontaneously reported cases from health professionals, non-healthcare professionals, health authorities, or the medical literature, data lock point: 15 July 2007), 884 cases of overdose were identified.

Of the 884 cases identified, 165 reported a first total daily dose >100 mg. Events that showed a significant increase (≥2 times) in all overdose cases vs. overall sildenafil dataset were accidental overdose, drug administration error, intentional overdose, overdose, erection increased and priapism. The following AEs showed a significant increase (>2 times) in overdose cases with a first total daily dose > 100 mg vs. all

overdose cases and/or all sildenafil cases: acute myocardial infarction, myocardial infarction, tachycardia, death, drug interaction, malaise, dyspnoea and hypotension.

Of the 884 cases identified, 57 of these reported death as an outcome.

**Drug Abuse**

- *Abuse*

From post-marketing data, 51 cases of abuse (recreational use of a drug) were identified representing a reporting rate of 0.13% (51/39,277).

Nine of them reported abuse with illicit drugs (e.g. methamphetamine, cocaine, marijuana). In eight of these cases, there was no indication that sildenafil was also abused with these illicit drugs. In the ninth a teenage patient died while taking sildenafil, cocaine and/or marijuana. Of the remaining 42 cases, only 5 (11.9%) reported serious events, one of these cases having an outcome of death (a patient with a non-ST segment myocardial infarction who died "a couple of days" after undergoing percutaneous transluminal coronary angioplasty).

At least 32 (indication was unknown in five cases) of the 42 cases of sildenafil abuse described patients who did not have ED. In addition to Drug abuser, the most frequently reported PTs in these cases were Drug ineffective (19 cases), Nasal congestion (5 cases), Erythema (5 cases) and Somnolence (4 cases).

- *Misuse (defined as intentional incorrect administration/use of a drug on the part of the patient/consumer or the health care provider)*

From post-marketing data, a total of 535 cases were identified representing a reporting rate of 1.4% (535/39,277). Events that showed a significant increase (>2 times) in the misuse dataset vs. the overall dataset were pregnancy and erection increased. All of the 11 cases reporting pregnancy originated from literature reports.

The most common type of misuse reported was in patients taking sildenafil who did not have a proper diagnosis of MED, did not receive the drug from a medical professional or through prescription, and/or were taking sildenafil for recreational purposes.

- *Dependence (habitual psychological and physiological dependence of a substance that is beyond voluntary control*

From post-marketing data, a total of 59 cases of dependence were identified representing a reporting rate of 0.15% (59/39,277). Of the 59 cases, 42.4% (25/59) contained serious events, none of which resulted in death.

- *Inadvertent/Unintentional Incorrect Use (accidental administration/accidental maladministration/ accidental use of the product outside of labelling or prescription on the part of the health care provider or the patient/consumer)*

From post-marketing data, a total of 357 cases were identified from a database of 39,277 non-clinical study sildenafil cases received through 15 July 2007, representing a reporting rate of 0.91% (357/39,277).

Of the 357 cases identified in this search, 15.4% (55/357) of them contained serious events, four of which resulted in death.

The most frequently reported PTs were drug ineffective (150 cases), intentional overdose (64 cases), Flushing (29 cases), Erectile dysfunction (26 cases), Erection increased (26 cases) and Headache (26 cases).

Following the assessment of these data, the CHMP considered that the proposed risk minimisations activities were unlikely to ensure self assessment and correct use of the product, in the absence of medical supervision.

The CHMP had major concerns, particularly related to the cardiovascular risk and the ability of the patient to self diagnose the erectile dysfunction (ED) condition and the underlying causes/conditions. In response to these major objections, the MAH further elaborated on the proposed risk minimisation measures.

**Proposed risk minimisation measures**

*Cardiovascular risk*

The MAH proposed that the risk minimization measures include clear identification of patients who can safely commence or restart sexual activity in the non-prescription setting as defined by a treatment algorithm. This is aimed at enabling both the pharmacist and the patient to effectively identify i) cardiovascular conditions considered not suitable for treatment with Viagra 50 mg non-prescription and ii) patients who are at high cardiac risk for initiating or restarting sexual activity.

Furthermore, the Product Information has been strengthened for the non-prescription setting by highlighting cardiovascular conditions considered not suitable for Viagra 50 mg non-prescription and providing clear instruction to consult with a physician.
The text on the packaging will also clearly warn patients not to take Viagra if they are not fit enough for sex.

The MAH also proposed additional country-specific advice around consultation with the pharmacist are proposed to be added within the blue box, as best applicable according to pharmacy practice in each country of the EU.

Additional risk minimisation measures are also proposed to enable the pharmacist and the patient himself to easily identify cardiovascular conditions considered not suitable for treatment with Viagra 50 mg non-prescription. The MAH believed that the risk minimisation measures will accommodate divergent pharmacy practices across the European Union (EU) and offer individual countries the flexibility to implement measures according to local needs, guidelines and pharmacy practice. In addition, all risk minimisation measures highlight the importance of regular health checks and education about the potential cardiac risks associated with sexual activity and potential associated cardiovascular disease.

The MAH is also of the opinion that pharmacy based supply of Viagra 50 mg non-prescription supplements the current MED medical model by i) facilitating access for men seeking treatment for MED, ii) raising awareness to MED and appropriate use of Viagra, and iii) providing access to legitimate supply of quality product within the healthcare setting and iv) raising awareness of MED and its associated conditions.

**Discussion on the RMP**

*Cardiovascular risk*

In order to circumvent the need for medical supervision, the MAH proposed a treatment algorithm that defines suitable and unsuitable patients for sildenafil 50 mg non-prescription and predicts the cardiovascular risk.

In this algorithm, the cardiovascular fitness for initiating or resuming sexual activity will be assessed through a simple assessment of exercise ability reported by thepatient. .
No exercise test is going to be performed but patients are going to be simply asked about their exercise capacity when they are in a theoretical effort situation in their normal life. As there is no standardization either of this effort or the way of measuring it, the CHMP is of the opinion that it appears impossible to draw any firm conclusion on the cardiovascular risk from the patients' responses. This would be especially

relevant in the case of patients who do not refer to any symptoms and would accordingly be classified as low cardiovascular risk.

The CHMP emphasized that there is growing evidence that ED is strongly associated with the presence of overt and silent coronary artery disease (CAD) in both diabetic and non-diabetic patients. In this regard, the Second Princeton Consensus Conference clearly concluded that ED is a warning sign of vascular disease and that all men with ED and no cardiac symptoms need a detailed cardiac assessment, measurement of blood pressure, fasting lipid profile and glucose as well as lifestyle advice regarding weight and exercise.

In the CHMP opinion, the suitability of this questionnaire is thus more than doubtful. The CHMP has major concern on how the "responses to a few simple questions" (as claimed by the MAH) can replace medical judgment and appropriate tests. The CHMP believes that the use of this questionnaire without an appropriate medical assessment could end up in a misclassification of patients with cardiovascular risk. Furthermore, it is clear from the CHMP's view that the user will most likely not be able to give an objective assessment of his own achievement, not only for the interpretation of the test but for the whole proposed algorithm.

Notwithstanding the CHMP opinion that without medical supervision the cardiovascular risk cannot be determined, a proposal on the conditions under which the various tests should be executed and controlled and more elaborated information on the predictive value of the outcome to assess cardiovascular risk should be provided by the MAH.

*Self assessment*

Apart from the fact that an exercise test is not validated to assess the cardiovascular risk, the CHMP also considered that the proposed testing should be controlled by certified personnel, for example a physician.

The CHMP considers the proposed role of the pharmacist inappropriate. Given that pharmacy practice is very different across Europe, it seems difficult that the MAH is able to accommodate the proposed risk minimisation measures to local practices and local requirements in all the Member States. In addition, the CHMP is of the opinion that the proposed training programme for pharmacists is inadequate for providing all the necessary skills to identify potential underlying conditions, risk factors or concomitant medical conditions which require special attention or referral to a physician. It appears to be a highly demanding programme with respect to qualified personnel and time devoted to each dispensation. Furthermore, in most cases pharmacies lack conditions for guaranteeing the privacy that is required for any medical evaluation. The MAH's assumption that ED patients will be more comfortable in an open setting like a pharmacy is not shared by CHMP. The MAH intends that Viagra non-prescription will be supplied only to pharmacy retailers and not to non-pharmacy retailers. How this can be guaranteed by the MAH is unclear. From the CHMP's point of view, the implementation of such a programme is unrealistic and could result in a non-compliance to the programme.

With respect to the self diagnosis of the ED, it is important to emphasize that underlying problems, such as anatomical or structural problems, post-traumatic arteriogenic ED in young patients and hormonal causes (hypogonadism, hyperprolactinemia) do not require pharmacological treatment as they can be cured with specific interventions (like by-pass surgery or hormonal replacement). Thus, oral PDE5 inhibitors can be prescribed as a first option once the need of other therapeutic alternatives have been ruled out, specifically when the psychological cause has been excluded and the ED is considered of organic origin.

*Indirect danger*

With respect to the self diagnose of other underlying causes/conditions, erectile dysfunction may be the presenting symptom of serious medical problems that needs to be evaluated before treatment is started. Thus, the CHMP considers that without medical supervision, sildenafil can mask the (first) symptom of serious underlying conditions. The diagnosis of ED thus implies a proper medical history, a physical examination,

laboratory tests (if appropriate) and the selection of the best treatment for each patient (pharmacological and/or non pharmacological treatment). The objective of the diagnostic workup is, therefore, to differentiate psychological causes of ED from organic causes of ED in order to recommend the most appropriate treatment. Inevitably a treatment with a PDE5 inhibitor without medical examination could lead to a delay in diagnosis, or even to a lack of diagnosis, of the underlying disease that may be detrimental for the patient.

A lack of argumentation from the MAH's responses still makes unclear how this delay will influence the development of the underlying cause.

*Increased risk of incorrect use*

With respect to the risk of incorrect use, the special case of young patients has not been addressed by the MAH. Importantly, the use of sildenafil for the treatment of ED in these patients as well as the recreational use should be considered.

Having considered the proposed RMP measures, the CHMP is still of the opinion that the risk of misuse may increase if Viagra 50 mg is used without medical supervision. The CHMP considers that the proposed risk minimisation activities related to the pharmacist training program and pharmacy guidance (i.e treatment algorithm) and the further SPC, Labelling, Package Leaflet risk minimisations are unlikely to ensure self assessment and correct use of the product, in the absence of medical supervision. Initial major objections and concerns raised by CHMP in this respect therefore remain to be addressed.

## III.4 Regulatory aspects

According to the European Commission guideline on *'Changing the classification for supply of medicinal product for human use'* (January 2006), the MAH proposed to change the classification of Viagra 50 mg from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription'.

The MAH considers that the criteria for medical prescription under article 71 of the Directive 2001/83/EC, as amended, are not met for Viagra 50 mg.

Having considered the overall benefit-risk of Viagra and the MAH's responses to the Request for Supplementary Information (EMEA/CHMP/11919/2008), the CHMP still considers that:

- The interaction with nitrates can represent a direct danger. Currently sildenafil is contraindicated in patients taking nitric oxide donors and nitrates;
- Sildenafil used as a symptomatic treatment by the patient, can delay diagnosis and definitive treatment of underlying pathologies(vascular disease, hypertension, hypercholesterolemia and diabetes) and jeopardise the chance of more successful therapy;
- Full medical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered. As a result, the patient's ability to self diagnose the possible underlying causes is of major concern;
- The increased risk of misuse remains a major concern, particularly in young patients;
- The dosage adjustment required in certain patient populations reinforce the need for medical supervision prior treatment initiation with sildenafil;

The MAH is thus required to demonstrate that the product can be used efficaciously and safely in accordance with the European Commission guideline *'Changing the classification for supply of medicinal product for human use'* (January 2006), without substituting the role of the physician by the pharmacist. Importantly, the written (package leaflet and label) information should be sufficient so that it substitutes for the absence of medical supervision.

Having considered the above, the CHMP is of the opinion that the first and second criteria for medical prescription under Article 71 of the Directive 2001/83/EC, as amended, are met for Viagra 50 mg and therefore cannot recommend at the present time, the change of the classification of Viagra 50 mg to 'medicinal product not subject to medical prescription'.