MHRA PUBLIC ASSESSMENT REPORT

Statins: updates to product safety information

November 2009

EXECUTIVE SUMMARY

(Please note that this summary is intended to be accessible to all members of the public, including health professionals)

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports we discuss the evidence for a safety issue with a particular drug or drug class. This MHRA Public Assessment Report discusses a review of the safety information for a class of medicines called statins[a].

Statins are widely used to treat patients with high levels of cholesterol and triglycerides (fats) in the blood. These fats can become deposited on the walls of blood vessels in the body, causing them to narrow and harden. This can lead to heart disease and an increased risk of heart attacks and strokes. Lowering the body's cholesterol levels with statins therefore reduces the risk of having major cardiovascular events, such as heart attacks and strokes.

The statins licensed for use in the UK include: atorvastatin (brand name Lipitor); fluvastatin (Lescol, Lescol XL); pravastatin (Lipostat); rosuvastatin (Crestor); simvastatin (Zocor, Zocor Heart-Pro, Inegy)

As with any medicine, the use of statins may lead to adverse reactions (side-effects) in some individuals. Evidence suggests that the use of statins may be associated with certain adverse reactions, such as sleep disturbances[b], memory loss, micturition disorders[c], sexual disturbances[d], depression and interstitial pneumopathy[e].

A Europe-wide review conducted by the MHRA assessed the evidence available on all of the above adverse reactions with the use of the following statins: atorvastatin; fluvastatin; lovastatin[f]; pravastatin; rosuvastatin; and simvastatin. The evidence assessed included data from clinical trials, post-marketing reported cases of the adverse reactions, and published literature. A summary of the assessment, and the consequent changes to product information for all statins are presented in the following report.

Results and Conclusions

The review considered the evidence on the adverse reactions for each individual statin medicine, and for the statin drug class as a whole. Based on the evidence in the review, it was decided that the following adverse events were a class effect of statins as a whole: sleep disturbances; memory loss; sexual disturbance; depression; interstitial pneumopathy. The review also concluded from the evidence that micturition disorders did not need to be added to product information for the whole statins class at the present time. On this basis, the review recommended that the safety wording in product information (Summary of Product Characteristics [SPC] and patient information leaflets) for all statins should be updated accordingly.

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[a] Also known as HMG CoA reductase inhibitors
[b] Including insomnia (inability to sleep) and nightmares
[c] Difficulties with urinating
[d] Difficulties with having sex
[e] Injury to the lung tissue that leads to breathing problems
[f] Not available in the UK

Outcome

The safety product information for all statins will be updated as follows:

<u>Core SPC warnings:</u>

Section 4.4 – Special warnings and precautions for use

<u>Interstitial lung disease</u>
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Section 4.8 – Undesirable effects

The following adverse events have been reported with some statins:
- Sleep disturbances, including insomnia and nightmares [where this is not already listed]
- Memory loss
- Sexual dysfunction [where this is not already listed]
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

<u>Patient Information Leaflet:</u>

Check with your doctor or pharmacist before taking [statin] if you:

- Have severe respiratory failure

Possible side effects

- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual difficulties
- Depression
- Breathing problems including persistent cough and/or shortness of breath or fever

1. INTRODUCTION

(See glossary for explanation of terms used in this document)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports we discuss the evidence for a safety issue with a particular drug or drug class. This MHRA Public Assessment Report discusses a review of the safety information for HMG CoA reductase inhibitors (which will be referred to as statins for the remainder of the report).

Statins are effective and widely-used treatments for patients with hypercholesterolaemia, and for the prevention of cardiovascular events. However, as with any medicine, the use of statins may also lead to adverse drug reactions (ADRs) in some individuals. Accumulating information from reported cases[a] and published medical literature suggested that the use of statins is related to potential signals[b] for the following adverse effects: sleep disturbances; memory loss; micturition disorders, sexual disturbance; depression; and interstitial pneumopathy.

On the basis of this information, the MHRA reviewed clinical trial data, cases reported after marketing and literature on the use of statins with occurrences of the following potential adverse events:

- **Sleep disturbances (including insomnia) and parasomnia**

Background: Parasomnias are disorders characterised by abnormal behaviour or psychological events occurring in association with sleep. The Diagnostic and Statistical manual of Mental Disorders, Fourth edition, states that there are four major types of parasomnia, including nightmare disorder, sleep terror disorder, sleepwalking disorder and unspecified parasomnia. Established risk factors for parasomnia are mental health problems, psychological stress, personal trauma, younger age, sleep deprivation, shift work and alcohol consumption [1,2].

The prevalence of parasomnias varies between countries and survey populations, with 2%, 4% and 12% of the survey populations from the United Kingdom, Finland and Spain, respectively reporting occurrences[3, 4, 5].

General estimates of the prevalence of insomnia range from 10%–48% depending on the definition used and the time frame examined[6, 7].

- **Memory loss**

Background: Memory loss is a common subjective complaint mostly seen in the elderly. The prevalence of age-associated memory impairment based on pooled data gathered from standard clinical memory tests was 41% for persons aged 50–59 years, and 52% for those aged 60–69 years. More severe forms of memory impairment, such as those seen in Alzheimer's disease, were found to affect 5%–10% of persons aged 65 years or older[8].

- **Micturition disorders (frequency, nocturia, dysuria)**

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[a] Suspected adverse drug reactions to any medicine in the UK can be reported to the MHRA through our Yellow Card Scheme (www.yellowcard.gov.uk)

[b] An indicator or reported information that suggests that a drug may be associated with a previously unrecognised ADR or an existing ADR that is different from current expectations

Background: Micturition disorders include disorders of urine storage and voiding, caused by a lack of voluntary control of urine elimination from the bladder. Considerable changes in the morphology and innervation of the detrusor muscle of the bladder, and changes in bladder metabolism are seen with aging, which can cause urinary dysfunction and lower urinary tract symptoms[9]. Established risk factors for micturition disorders are older age, hypertension, cardiovascular disease, diabetes mellitus and benign prostatic hyperplasia (BPH)[10,11,12].

The prevalence of overactive bladder syndrome (a common type of micturition disorder) was 16%–17% when measured in sample populations of adults in the United States[13] and six European countries[14].

- **Sexual disturbance**

Background: The causes of male erectile dysfunction are multifactorial. The prevalence of this condition in the United States was 52% in a large sample population from a study of males aged 40–70 years. Erectile dysfunction was more prevalent in the older study participants and in those with chronic conditions such as diabetes mellitus, and was associated with a variety of medications including drugs for heart disease, hypoglycaemia and hypertension[15].

- **Depression**

Background: Depressive disorders come in different forms. Three of the most common types of depressive disorders are major depressive disorder; dysthymia; and bipolar disorder. The risk factors associated with depressive disorders include a family history of depression, female gender, severe or chronic illness, a marital status of widowed, separated or divorced; lack of social support; negative stressful events; and chronic stress[16, 17, 18].

The estimated point prevalence for depressive episodes in a survey on adults aged 16–74 years in the UK in 2000 was 2·6%; for the category of 'mixed depression and anxiety' in the same survey, the estimated point prevalence was 11·4% (from the National Institute for Health and Clinical Excellence 2009 guidelines on treating depression). The US National Comorbidity Survey Replication conducted between 2001–2003 reported the 12-month prevalences of major depressive disorder, dysthymia, and bipolar disorder were 7%, 2%, and 3%, respectively[19]. The lifetime prevalences of these disorders were 17%, 3%, and 4%, respectively[20].

- **Interstitial pneumopathy**

Background: The term 'interstitial lung disease' (ILD) encompasses a group of disorders that have been classified together because of similarities in clinical, radiological, physiological and pathological manifestations. Sarcoidosis, idiopathic pulmonary fibrosis (IPF) and pulmonary fibrosis associated with connective tissue disorders are the most common interstitial lung diseases of unknown origin. Risk factors for the development of IPF include cigarette smoking; in addition, numerous medications have been associated with ILDs, including (but not limited to) antibiotics (penicillins, sulfonamides), anti-inflammatory agents, chemotherapeutic agents (bleomycin, busulfan, cyclophosphamide), narcotics, and select cardiovascular agents such as amiodarone, beta-blockers, and hydrochlorothiazide[21, 22]. There have also been a small number of published case reports involving the use of simvastatin, lovastatin, and pravastatin and development of ILDs[23, 24, 25].

Overall, the review was to address causality for each event (time to onset, de-and re-challenge, presence and absence of confounding factors) and whether the ADRs were dose-related. With regard to sleep disturbances specifically, the review was to address

whether events of sleep disturbance were related to the timing of statin dose administration (ie, morning or evening)or related to the timing of statin dose administration (ie, morning or evening). With regard to memory loss, the review was to address whether events of memory loss with use of statins was short or long term, and whether the memory loss was reversible. With regard to interstitial pneumopathy, the review was to address the need or use of corticosteroids.

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2. SUMMARY OF DATA:

2.1 Sleep disturbances (including insomnia) and parasomnia

In a general literature search, six randomised controlled trials (RCTs), with study durations of 3–152 weeks, as well as three case reports involving four patients were identified, published between January 1966–April 2006.

No relationship between statin use and sleep disturbance was found in four of the six RCTs reviewed. One RCT comparing lovastatin to pravastatin on sleep efficiency and sleep stages, found patients in the lovastatin group to have an increase in wake time after sleep onset. A second RCT reported that patients on dietary or statin therapy had less difficulty falling asleep than did those on non-statin lipid-lowering agents. None of the RCTs reported true parasomnia.

Atorvastatin:
Insomnia already is listed as a common adverse event (experienced by ≥ 1% of patients in clinical trials) in the S P C, as a previous review of available data has concluded that a causal association is possible.

There was no clear association between atorvastatin use and incidence of parasomnia-related events in atorvastatin clinical studies. The incidence of parasomnia-related events was low (<0.8%) and generally was balanced among treatment groups.

There were 242 reports of parasomnia related cases with atorvastatin use from both clinical trials and post-marketing. Of these 91 cases of had dechallenge information, atorvastatin appeared to be the most likely cause of the parasomnia event in 40 cases. Seventy-two of the 91 cases reported a positive dechallenge (ie, the event resolved when the drug was discontinued), and 18 cases reported a positive dechallenge and rechallenge (ie, the event resolved when the drug was discontinued, and occurred again when the drug was re-administered). A brief review of the remaining cases revealed that seven cases reported a medical history that included parasomnia-related events, including three cases reporting them in association with previous use of other statins. Overall, an assessment of the safety database for atorvastatin suggests the possibility of an association between atorvastatin use and parasomnia-related events.

Fluvastatin:
Insomnia is already listed in the SPC (as a previous review of available data has concluded that a causal association is possible). A case of insomnia associated with fluvastatin was identified in the literature search[26] .

The estimated incidence rates regarding sleep disturbance adverse events (AEs) in clinical trials (with insomnia constituting the majority of reports), were higher on fluvastatin than on placebo: 1.1(95% confidence intervals [CI], 0.9-1.3) versus 0.6 (95% CI, 0.5-0.8) per 100 patient-years, respectively. Two cases of sleep disturbances were reported in s study comparing morning to evening regimens of fluvastatin (Lescol XL) 80mg.

Of the 258 medically-confirmed post-marketing reported cases of sleep disturbances with fluvastatin use, 107 contained dechallenge information (92 reports of positive dechallenge, and 15 reports of positive rechallenge). Many of the 258 reports were for insomnia (149); the others were: somnolence (36), sleep disorder (28) and nightmare (9). Of the 92 reports of positive dechallenge with fluvastatin, 47% (44) were related to insomnia; of the 15 positive rechallenges with fluvastatin, 80% (12) were related to insomnia.

Lovastatin:
Two article on lovastatin and sleep disturbance were identified by a literature search: one which compared the effects of lovastatin to those of pravastatin on sleep patterns and psychomotor performance; the authors concluded that neither drug had significant effects on either sleep or CNS functions[27] Another article referred to a double-blind, placebo-controlled, cross-over study comparing the effects of lovastatin, pravastatin and placebo on sleep[28]. Marked treatment differences were noted ; all changes indicated improved sleep with lovastatin compared with pravastatin, and there were no differences with either drug or placebo.

The largest amount of clinical data on lovastatin for sleep disturbances is from 2 trials: 1) The Expanded Clinical Evaluation of Lovastatin (EXCEL) trial[29]; and 2) The Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels (AFCAPS/TexCAPS) trial[30]. Nine of 6582 (0·1%) patients discontinued the first clinical trial because they experienced sleep disturbances while taking lovastatin; only 2 of 1663 (0·1%) patients discontinued while taking placebo. In the second trial, 13 of 3304 (0·4%) patients receiving lovastatin experienced sleep disturbances, 11 of 3301 (0·3%) patients experienced sleep disturbances with placebo.

A total of 21 postmarketing reported cases of sleep disturbances were reported between 21 July 1987–31 December 2005, one with a positive rechallenge. The sleep disturbances reported were: abnormal dreams (18), nightmare (4), sleep disorder (3), insomnia (2).

Pravastatin:
The pravastatin SPC already lists sleep disturbances and insomnia as potential ADRs with pravastatin use, as a previous review of available data has concluded that a causal association is possible. A literature search identified 3 publications which were important with regard to a relationship between pravastatin therapy and parasomnia: The first study noted that hypercholesterolaemic patients who received pravastatin and lovastatin experienced insomnia. The subjects had moderate sleep disturbances that could account for insomnia; these sleep disturbances most likely predated the use of the statins[31]. The second study concluded that there were no significant effects of lovastatin or pravastatin on sleep and cognitive performance[27]; however, the third study showed that sleep EEG measures relevant to insomnia provided evidence of significant differences in terms of entries and latency to stage I sleep between patients treated with pravastatin (40mg/day), simvastatin (20mg/day) and placebo[32]. .

Data from the long-term, placebo-controlled pravastatin clinical studies WOSCOPS[33], CARE[34], LIPID[35] and PROSPER[36], as well as the active-controlled PROVE-IT[37] study was examined. In the WOSCOPS, CARE, LIPID and PROSPER studies, the incidence of parasomnias was similar in pravastatin-treated and placebo-treated patients. In the active-controlled PROVE-IT study, the incidence of parasomnias was similar in the pravastatin and atorvastatin arms. In the pravastatin-treated patients, incidence of parasomnias ranged from 0.1% (LIPID) to 12.1% (CARE); the inter-study variability can be explained by differences in patient population and study duration. The majority of parasomnias were reported as 'sleep disturbances'.

Ninety post-marketing reported cases of parasomnia (seven classed as serious) were received between 31 March 1989–31 January 2006, which included pravastatin as a suspect or interactive drug. Fifteen patients experienced parasomnia when pravastatin was taken in the evening. In five of the 15 patients, the event resolved when the dosing regimen was changed to morning. The dosing regimen was not specified for the remaining 75 patients. Dechallenge was indicated in 36 reports; there was

improvement in 35 reports and no improvement in one report following dechallenge. Of the 35 reports noting improvement on dechallenge, 11 reports indicated rechallenge (nine positive and two negative).

Rosuvastatin:
There were no publications regarding rosuvastatin and sleep disturbances in the literature.

In clinical trial data, the incidence rate of all sleep disturbances combined with rosuvastatin use was 55·1 per 1000 patient-years. Highest incidence rates were observed for insomnia (48·7 per 1000 patient-years), sleep disorders (3·0 per 1000 patient-years), nightmares (2·1 per 1000 patient-years), and abnormal dreams (0·9 per 1000 patient-years). Incidence rates were comparable to incidence rates for other statins.

There were 113 medically confirmed reports of sleep disturbances with rosuvastatin use from both clinical trials and post-marketing. Most reported insomnia (n=72), nightmares (n=20), general sleep disorders (n=17), and abnormal dreams (n=8). No conclusions could be drawn on a possible relation to timing of dose administration as this information was limited; in six cases, rosuvastatin was initially given in the evening. Three cases of insomnia had a positive rechallenge, and 35 had a positive dechallenge.

Simvastatin:
Seven studies were identified in the literature. Three randomised, placebo-controlled studies concluded that simvastatin did not cause a difference in sleep duration[38], sleep or cognitive performance[39], and did not adversely affect measures of sleep disturbance[32]. In addition, answers from a questionnaire indicated that the incidence of significant sleep disturbances is no different whether the patient is taking simvastatin, treated by diet alone, other statins, or non-statin medication[40]. However, three other publications showed that patients treated with simvastatin had sleep interruptions[41], sleep disturbances[42], and new-onset nightmares and restless nights[43].

The following number of patients experienced sleep disturbances in four clinical trials with simvastatin versus placebo: 112 vs 108 in the 4S trial[44]; four vs 10 in the MAAS trial[45]; seven vs four in the HPS trial[46]; and eight vs five in the A to Z trial[47].

The majority of post-marketing reported cases of 'sleep disorders' were for insomnia. The causality of simvastatin cannot be ruled out, as a positive dechallenge and a positive rechallenge were reported. Of the reports that met the criteria (approximately one-third in each case), the median time to onset for insomnia, parasomnia and sleep disturbance after treatment with simvastatin was 4, 1 and 3 days respectively.

There was little information regarding timing of dose. The reporting rate was highest for the 10mg and 20mg dose in each case but this does not identify a dose relation.

2.2 Memory loss

In a general literature search, a review addressed the incidence of statin-associated memory loss in several statin studies[48]including the Heart Protection Study. . The author concluded that:
-   As cholesterol synthesis is essential for neuronal function, greater attention to cognitive outcomes in patients receiving statins is warranted
- It would be beneficial for clinicians to be able to detect memory changes among their patients, and to routinely inquire about their mental health status
- Given the high background rate of memory loss in the population receiving statins, controlled studies comparing the effects of statins on cognitive functions are warranted.

Atorvastatin:
Memory loss (amnesia) is already included in the SPC for atorvastatin, as a previous review of available data has concluded that a causal association is possible.

Fluvastatin:
The literature search did not reveal any relevant publication or published case reports associating the use of fluvastatin with memory loss, and only one case of memory impairment occurred in the clinical trials, in a patient on placebo. However, there were 40 medically-confirmed post-marketing reported cases of memory loss with fluvastatin use (14 serious, 26 non serious); 14 with limited information, and 14 with an alternative explanation. Fifteen reports were associated with 20 mg, 14 with 80 mg, four with 40 mg;the dose was unknown in 7 cases. The time to onset of memory loss was reported in 50% (20) of cases, and varied between one day and three years. 25% (10) of reports occurred in less than 1 month. A positive dechallenge was reported in 27% (11) of cases.

Lovastatin:
To assess the frequency of memory loss in clinical trial data, two trials were considered:
1) Expanded Clinical Evaluation of Lovastatin (EXCEL) trial[29] and
2) Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels (AFCAPS/TexCAPS) trial[30]. In the first trial, five of 6582 (0.1%) patients experienced memory loss while taking lovastatin, compared to one of 1663 (0.1%) patients who experienced memory loss with placebo. In the second trial, four of 3304 (0.1%) patients experienced memory loss with lovastatin, compared with no patients experiencing memory loss with placebo.

A total of 71 post-marketing cases of memory loss with lovastatin use were reported between 21 July 1987–31 December 2005. The most frequent reports were of memory impairment (55), amnesia (16), dizziness and insomnia. There were six positive rechallenges in these cases, which is a strong element to support a causal relationship.

Pravastatin:
The literature search identified two papers which, in particular, were most important with regard to a relationship between pravastatin therapy and memory loss. The first focused on pravastatin, simvastatin and atorvastatin[48]. The authors concluded that a consistent effect of statins on memory loss is not supported by the current literature; however case reports raise the possibility that statins, in rare cases, may be associated with cognitive impairment, although causality is not proven. In the second publication the authors concluded that neither lovastatin nor pravastatin impaired daytime cognitive performance after 4 weeks of treatment in patients with primary hypercholesterolaemia[49].

In the WOSCOPS[33], CARE[34] and PROSPER[36] clinical studies (see section 2.1 for details of the studies), the incidence of memory loss was similar in pravastatin-treated and placebo-treated patients. In the active-controlled PROVE-IT[37] study, the incidence of memory loss was similar in the pravastatin and atorvastatin groups. There were no reports of memory loss in the LIPID[35] study. In pravastatin-treated patients, incidences of memory loss ranged from 0.4% (WOSCOPS) to 2.8% (CARE); the inter-study variability can be explained by differences in patient population and study duration.

During the period 31 March 1989–31 January 2006 there were 117 post-marketing reported cases of memory loss (23 serious) which included pravastatin sodium as a suspect or interactive drug. Eighteen patients experienced short-term memory loss and 3 patients experienced transient global amnesia. The type of memory loss was not specified for the remaining patients. No cases of long-term memory loss were reported. Dechallenge to pravastatin was indicated in 33 reports with positive dechallenge in 27 reports. Of the 27 reports with positive dechallenge, 4 reports also indicated a positive rechallenge. In nine cases pravastatin therapy was continued following the memory loss event; two reported improvement, four did not improve and three outcomes were not reported).

Rosuvastatin:
A Canadian publication was found in the literature search that presented a brief review on 19 case reports of amnesia[50]. Of these 19 reports, four were associated with rosuvastatin use. A positive dechallenge was mentioned for two of the rosuvastatin cases with no further details.

The incidence rate of memory loss from the clinical trial data was 3–0 per 1000 patient-years for rosuvastatin, which was comparable to the incidence rate reported for other statins. No cases of memory loss were reported in the placebo group.
There were 41 medically-confirmed post-marketing reported cases of memory loss. Information on time to onset was known in 16 case reports and ranged from 2–210 days. The majority of cases (56%) occurred within the first month of rosuvastatin treatment. No dose relationship was observed. Six of the medically-confirmed reports described short-term memory loss or transient global amnesia. The type of memory loss was not specified in the remaining reports. Outcomes for the events were known in 21 case reports; in 19 of these cases (90.4%), patients recovered or were recovering. In 12 cases memory loss seemed to be reversible after discontinuation of rosuvastatin. Two cases had a positive rechallenge, but provided insufficient information to determine a causal relationship. There were 10 reports of a positive dechallenge.

Based on the data provided, the rosuvastatin SPC should be updated to include this adverse event.

Simvastatin:
In clinical trials the incidence rates of memory loss observed were similar between simvastatin and placebo[51,44,45].

A total of 333 cases of memory loss were reported post-marketing. Seven of the 333 ADRs demonstrated positive rechallenge, while 3 recorded a positive dechallenge. With 85 reports describing resolution of symptoms following withdrawal of simvastatin and 25 reports indicating persistence of symptoms, a causal relationship between simvastatin and memory loss cannot be ruled out.

2.3 Micturition disorders (frequency, nocturia, dysuria)

An extensive search for medical and scientific literature evaluating relationships between statin use and micturition disorders yielded no relevant results.

Atorvastatin:
Micturition-related event incidence was comparable between the atorvastatin and the placebo groups in all individual clinical studies that included placebo (CARDS, ASPEN, and ASCOT-LLA). Similar results were found for treatment-associated micturition disorder-related adverse events.

There were 31 post-marketing reported cases which reported a temporal relationship between atorvastatin initiation and onset of micturition disorder related-events;many of these cases reported either a positive dechallenge or rechallenge.

Fluvastatin:
In clinical trials, there were 66 (0.9%) cases of micturition disorders in fluvastatin patients and 39 (0.9%) in placebo patients. The most frequent AEs were dysuria and pollakiuria, followed by nocturia. The estimated incidence rates of micturition disorder-related adverse events, on placebo were 0.4 (95% CI, 0.3 - 0.5) and 0.6 (95% CI, 0.4 – 0.7) per 100 patient years on fluvastatin.

There were 155 medically-confirmed post-marketing reported cases of micturition disorder with fluvastatin use (84 serious, 71 non serious).
The most frequent reported AEs were pollakiuria (42), incontinence (32), dysuria (18), urinary retention (12), and nocturia (10). The time to onset of the AE was reported in 58% (109) of cases, and varied between few hours to five years. In 23% of cases, symptoms appeared within one month of taking fluvastatin. A positive dechallenge was reported in 27% (42) of cases including 21% (9) of positive rechallenge.

Lovastatin:
The largest amount of data on lovastatin for micturition is included in the two trials described in previous sections for other ADRs[29,30]. Six of 6582 (0.1%) patients discontinued the first trial due to experience of micturition disorders while receiving lovastatin, compared to one of 1663 (0.1%) patients with placebo. A similar number of patients experienced micturition disorders with both lovastatin and placebo in the second trial.

A total of 62 post-marketing cases of micturition disorders were reported between 21 July 1987–31 December 2005. There were 11 positive rechallenges, one negative rechallenge, 17 positive dechallenges and three negative dechallenges. The reported micturition disorders were: dysuria (16), nocturia (15), urinary incontinence (11), oliguria (8), urinary retention (7), micturition urgency (3) and general micturition disorder (3).

Pravastatin:
Abnormal urination (including dysuria, frequency, nocturia) is already contained in section 4·8 of the pravastatin SPC, as a previous review of the available data has concluded that a causal association is possible.

Rosuvastatin:
The incidence rate of micturition disorders in the clinical trial data was 24·8 per 1000 patient-years. Highest incidence rates were observed for pollakiuria (10·6 per 1000 patient-years), dysuria (3·9 per 1000 patient-years), nocturia (3·9 per 1000 patient-

years), and urinary incontinence (3·6 per 1000 patient-years). Incidence rates were comparable to incidence rates for other statins.

A total of 51 medically-confirmed post-marketing cases of micturition disorders were reported, the majority of which were pollakuria (n=23) and dysuria (n=15). Four reports with a positive rechallenge were described.

Simvastatin:
There were reports of micturition adverse events in 3 studies with simvastatin, including the 4S trial[51, 46, 47]

There were 141 post-marketing cases of micturition disorder reported. Sixteen of the 141 reports demonstrated positive rechallenge, and 53 recorded a positive dechallenge.

2.4 Sexual disturbance

A case-control study reported in the literature showed that forty-one (12.1%) patients receiving lipid-lowering therapy reported erectile dysfunction compared with 19 (5.6%) controls (p=0.0029). The authors concluded that statins were significantly associated with erectile dysfunction (p=0.009 and p=0.02, respectively) [52]. Another publication (a systematic review) concluded that there was evidence to suggest that statins may cause erectile dysfunction[53].

Atorvastatin:
Sexual dysfunction (impotence) is already listed in the SPC for atorvastatin, as a previous review of available data has concluded that a causal association is possible.

Fluvastatin:
One case of sexual dysfunction with fluvastatin was identified from clinical trials, regarding a patient treated with a combination of fluvastatin 80mg and a fibrate.

There were 82 medically confirmed post-marketing reported cases of sexual dysfunction with fluvastatin use (5 serious, 77 non serious). The most frequent reported AEs were erectile dysfunction (57), impotence (16), and decreased libido (7). Age was reported in 65% (53) of reports and varied between 33 and 69 years. In 35% of reports (19) patients were aged less than 50 years.
A positive dechallenge to fluvastatin was observed in 40% (33) of cases and a positive rechallenge to fluvastatin was reported in two cases.

Lovastatin:
To assess the frequency of sexual dysfunction in clinical trial data, two trials were considered, as in previous sections[29, 30]. Nine of 6582 (0.1%) patients experienced drug-related impotence after receiving lovastatin in the first trial, compared with no patients experiencing impotence with placebo (n=1663). Twenty-five (0.8%) patients had impotence with lovastatin use in the second trial; 23 (0.7%) had impotence with placebo in the same study.

A total of 413 post-marketing cases of sexual dysfunction and erectile dysfunction were reported between 21 July 1987–31 December 2005. There were 6 positive rechallenges to the drug, no negative rechallenges, 39 positive dechallenges and 20 negative dechallenges. The most frequently reported events were erectile dysfunction (149), decreased libido (32), sexual dysfunction (25), gynaecomastia (7) and decreased levels of blood testosterone (5).

Pravastatin:
Information on sexual dysfunction is already contained in section 4·8 of the pravastatin SPC, as a previous review of available data has concluded that a causal association is possible.

Rosuvastatin:
Clinical trial data showed that the incidence rate of sexual dysfunction was similar for rosuvastatin and all other statins combined (14·8 and 19·2 per 1000 patient-years, respectively). The incidence rate was higher for placebo, 54·0 per 1000 patient-years, but the absolute number of cases was low in this patient group (n=2).

There were 50 medically-confirmed post-marketing reported cases of sexual (erectile) dysfunction with rosuvastatin use . Time to onset varied from 3 days to 7 months. No cases of positive rechallenge were reported. A total of 18 cases had a positive dechallenge, but no reports showed a clear causal relationship.

Simvastatin:
In clinical trials with simvastatin, the following numbers of patients experienced sexual dysfunction or impotence with either simvastatin or placebo, respectively: 4S trial: 38 vs 26; MAAS trial: 1 vs 1; HPS trial: 7 vs 8; A – Z: 2 vs 6[51, 54, 44, 45].

A total of 413 post-marketing cases of sexual dysfunction with simvastatin use were reported. One hundred and twenty-eight of these patients had positive dechallenges, 26 patients had positive rechallenges, and four had negative rechallenges.

2.5 Depression

The literature review identified a large case control study[55] including 458 patients who were on statin therapy (atorvastatin, cerivastatin[a], fluvastatin, pravastatin, and simvastatin), and a prospective cohort study[56] including 140 and 219 patients who were on continuous and intermittent statin therapy, respectively, (atorvastatin, simvastatin, fluvastatin, lovastatin, cerivastatin, and pravastatin). Both studies demonstrated an association between statin use and a decreased risk of depression. The authors for the first article assumed that this could be explained by improved quality of life due to a decreased risk of cardiovascular events. However, the same study suggested that depression may be linked to low levels of plasma cholesterol[55].

Two articles were also identified that reviewed the possible link between serum cholesterol levels and depression. The authors conclude that available evidence does not support a clinically relevant link between reductions in cholesterol levels and mood disorder, or that cholesterol-lowering therapies increase the risk of depression and suicide.

Atorvastatin:
Depression-related event incidence was similar in the atorvastatin and placebo groups in all individual clinical studies that included placebo. However, in a post-hoc statistical analysis of the data in the BELLES[57] study, the difference in event incidence between the atorvastatin and pravastatin arms was statistically significant (p=0.039), although the patient numbers (305 and 309, respectively) and event numbers (6 and 0, respectively) in this study were small.

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[a] Withdrawn from the market worldwide in 2001

There were 136 post-marketing reported cases of depression with atorvastatin use, of which 115 cases reported a positive dechallenge. Sixteen of the 136 cases reported a positive dechallenge and rechallenge with atorvastatin.

Fluvastatin:
In clinical trials, there were 70 cases of depression in the placebo group and 87 cases in the fluvastatin group. Estimated incidence rates regarding depression AEs was similar in placebo and fluvastatin patients 0.7(95% CI, 0.5-0.9) versus 0.8 (95% CI, 0.6-0.9) per 100 patient years respectively.

There were 57 confirmed post-marketing reported cases of depression with fluvastatin use (40 serious and 17 non serious). 28 had insufficient information, and 9 had an alternative explanation or co-suspected medications.
Time to onset was available in 57% (33) of cases and varied between 48 hours and 4 years. A positive dechallenge was reported in 19% (11) of cases including two cases with positive rechallenge; ie, the patients experienced depression few days after fluvastatin initiation followed by positive dechallenge and a positive rechallenge.

Lovastatin:
To assess the frequency of depression in clinical trial data, two trials were considered (see section 2.1 for more details on these trials) [29, 30] . . Six of 6582 (0.1%) patients discontinued their participation in trial 1 because they experienced depression after taking lovastatin, compared to one of 1663 patients discontinuing due to depression after taking placebo (0.1%). In trial 2, the same number of patients experienced depression with lovastatin use and placebo (five of 3304 [0.2%] and five of 3301 [0.2%], respectively).

A total of 131 post-marketing cases of depression were reported between 21 July 1987–31 December 2005. There were seven positive rechallenges to lovastatin and one negative rechallenge, 40 positive dechallenges and two negative dechallenges. Specifically, the most frequent reports were of:depression (128), general symptom of depression (24) and mental disorder (19).

Pravastatin:
The literature search identified four papers which were most important with regard to a relationship between pravastatin therapy and depression. Three publications concluded that exposure to lipid-lowering drugs, statins (including pravastatin), or untreated hyperlipidemia did not increase the risk of depression or suicide[55,58,59]. The fourth publication concluded that although pravastatin and tocopherol did not adversely affect health-related quality of life in older patients with hypercholesterolemia, older patients have higher baseline levels of sleep dysfunction and cognitive impairment[60].

In the WOSCOPS[33], CARE[34], LIPID[35]and PROSPER[36] clinical studies (see section 2.1 for details of the studies), the incidence of depression was similar in pravastatin-treated and placebo-treated patients. In the active-controlled PROVE-IT[37] study, the incidence of depression was similar in the pravastatin and atorvastatin groups. In pravastatin-treated patients, incidence of depression ranged from 0.2% (LIPID) to 11.0% (CARE); the inter-study variability can be explained by differences in patient population and study duration.

During the period 31 March 1989–31 January 2006 140 post-marketing cases of depression (41 serious) were reported which included pravastatin as a suspect or interactive drug. A positive dechallenge to pravastatin was indicated in 57 reports, and a negative dechallenge was indicated in five reports. Of the 57 reports noting

improvement on dechallenge, 10 reports indicated rechallenge (eight positive and two negative). In seven cases, pravastatin therapy was continued following the event; two improved and five outcomes were not reported.

Rosuvastatin:
There were no publications identified regarding rosuvastatin and depression in the literature.

Incidence rates of depression obtained from clinical trial data were 30·3 per 1000 person-years for rosuvastatin, 26·3 per 1000 person-years for all other statins combined, and 13·0 per 1000 person-years for the placebo group.

There were 58 medically-confirmed post-marketing reported cases of depression. The time to onset of depression was within the first two weeks of treatment for 17 (56.7%) of the 30 cases which provided information on time to onset. A relatively high proportion of cases were associated with the 40 mg dose (12%). Three reports of depression had a positive rechallenge; however two cases were confounded and limited information was provided for the third case. Thirty-one cases had a positive dechallenge, one with a likely alternative cause.

Simvastatin:
A review of the literature did not support a link between the use of simvastatin or other cholesterol-lowering drugs and the increased risk of depression.

In clinical trials with simvastatin, similar incidence of depression has been reported between simvastatin and placebo patients[51, 60, 44, 45].

There were 54 post-marketing reported cases of depression classed as 'serious' in association with simvastatin use; the median time to onset of depression was 22 days (range 1 day to 2 years). Twenty of these cases indicated a positive rechallenge. The information regarding positive rechallenges indicates a link between simvastatin and depression.

2.6 Interstitial pneumopathy

Studies that looked at statins in general included two cohort studies, two preclinical laboratory studies, and three case studies involving 12 patients. A retrospective cohort study[61] that followed 787 patients with history of pneumonia found that those who had exposure to statins in general (n=110) versus those not exposed (n=677) had decreased 30-day mortality. Hypersensitivity pneumonitis or non-specific interstitial pneumonia has also been reported in association with lovastatin, pravastatin and simvastatin[24, 25]

Atorvastatin:
No studies involving atorvastatin that specifically examined interstitial pneumopathy were identified in the literature search.

Interstitial pneumopathy-related events that occurred in atorvastatin clinical trials were few and generally balanced among treatment groups.

There were 67 post-marketing reported cases of atorvastatin and interstitial lung disease (ILD);- in five of these cases, an association between atorvastatin and the ILD-related event could not be excluded.

Fluvastatin:
For fluvastatin, the literature search identified two cases of polymyositis with pulmonary fibrosis[62] . One additional case described fluvastatin associated with organising pneumonia[63].

There were no occurrences of interstitial pneumopathy identified in the clinical trial data. However, 23 medically-confirmed post-marketing reported cases of pneumonia have been reported with fluvastatin use; 10 reported a positive dechallenge to the drug.

Lovastatin:
To assess the frequency of interstitial pneumopathy in clinical trial data, two trials were considered (see section 2.1 for more details on these trials)[29, 30]. In trial 1, one of 6582 study participants experienced interstitial pneumopathy while receiving lovastatin and discontinued the trial because of this event; no participants receiving placebo experienced this adverse effect. There were no occurrences of interstitial pneumopathy in trial 2.

Fifteen post-marketing cases of interstitial pneumopathy with lovastatin were reported between 21 July 1987–31 December 2005. There are no data on rechallenges to lovastatin for any of the cases; however two cases had a positive dechallenge, and one case had a negative dechallenge. The most frequent reports terms were of: pulmonary fibrosis (7), pneumonitis (5), an increase in blood creatinine phosphokinase levels (2), interstitial lung disease (2), dermatomyositis (2), respiratory failure (2), vasculitis (2), lupus-like syndrome (2), alveolitis (1) and immune system disorders (1).

Pravastatin:
In the WOSCOPS[33], CARE[34] and PROSPER[36] clinical studies (see section 2.1 for details of the studies) the incidence of interstitial pneumopathy was similar in pravastatin-treated and placebo-treated patients. In the active-controlled PROVE-IT[37] study, the incidence of interstitial pneumopathy was similar in the pravastatin and atorvastatin groups. There were no reports of interstitial pneumopathy in the LIPID[35] study. The overall incidence of interstitial pneumopathy was very low, ranging from 0.1% (WOSCOPS, CARE and PROVE-IT) to 0.6% (PROSPER).

During the period 31 March 1989–31 January 2006 38 post-marketing cases of interstitial pneumopathy (37 serious) were reported which included pravastatin sodium as a suspect or interactive drug. Dechallenge to pravastatin was indicated in 16 reports; 10 were positive dechallenges and six were negative. Of the 6 negative dechallenge reports, one noted a negative rechallenge. In one case, pravastatin therapy was continued following the event and the outcome was reported as 'not improved'.

Rosuvastatin:
The clinical trial data did not show any reports of pneumonitis or pulmonary fibrosis in the rosuvastatin treatment group. One case of acute respiratory distress syndrome and one case of lung infiltration were reported in this group.

There were 4 medically-confirmed post-marketing reported cases of interstitial pneumopathy, specifically two serious reports of interstitial lung disease and two serious reports of pneumonitis. Time to onset of the adverse reactions varied between 17 days and 20 months after taking rosuvastatin. There were no reports with a positive rechallenge and 2 reports with a positive dechallenge.

Three of the four patients received treatment with steroids; 2 of these patients recovered, including the two cases with a positive dechallenge. The outcome for the third patient who continued rosuvastatin treatment was unknown.

Simvastatin:
Section 4.8 of the current SPC already contains reference to an apparent hypersensitivity syndrome, as a previous review of available data has concluded that a causal association is possible; some of the features listed; for example eosinophilia, are also pertinent in the case of interstitial pneumopathy.

The following numbers of patients experienced interstitial pneumopathy during clinical trials with simvastatin : 4S trial: 3 vs 1; HPS trial: 3 vs 12; A – Z: 1 vs 1 for simvastatin versus placebo, respectively[44, 46, 47].

There were 96 post-marketing reported cases of interstitial pneumopathy with simvastatin use. Of these 96 cases, 30 contained sufficient documentation to support the diagnosis of interstitial lung disease without the presence of confounding factors. In 23 of these 30 reports, treatment included corticosteroid therapy. There were no reports of positive rechallenge with simvastatin, but 24 positive dechallenges were indicated from the data.

While incidence of this event is very rare, it would be beneficial to include interstitial pneumopathy in the simvastatin SPC.

Recent evidence for interstitial lung disease with use of all statins
A recent systematic review[64] investigated the relationship between statins and ILD, by examining 14 cases published in medical literature and 162 reports retrieved from the FDA-AER database. The reports concerned all statins, although there was significant variation in the reporting rate among them, which probably reflected differences in prescribing and usage.

The authors note that the exact pathophysiology underlying possible statin-induced ILD remains unknown but suggest a number of potential mechanisms including: toxic lung tissue injury mediated by the inhibition of phospholipases as part of the statin effect on lipid metabolism; cytotoxicity triggered by disruption of mitochondrial function; or immune-mediated effects leading to oxygen-free radical production, cell injury and inflammation.

The review concluded that although the evidence is not definitive, ILD has been reported with most statins, suggesting a class effect. The review also concluded that clinicians should consider this possibility in patients on statins who present with symptoms and signs suggestive of ILD, and treatment should stop in any patient who has unexplained pulmonary symptoms and radiographic changes.

3. CONCLUSIONS

Sleep disturbances (including insomnia) and parasomnia:
The SPCs for atorvastatin and fluvastatin already contain insomnia as an undesirable effect in section 4.8, as a previous review of available data has concluded that a causal association is possible. The SPC for pravastatin also lists sleep disturbances and insomnia in the same section. The data from the clinical trials assessed in the review provided evidence that for some statins, the rates of sleep disturbances were higher than those seen in placebo-treated patients. (No dose relation could be identified from the data provided, and there was limited information regarding timing of dose).

When evaluating these differences between the members of the statin class it seems practical to include core safety information for sleep disturbances in all statin SPCs, as the data suggests there may be a class effect. Therefore, insomnia will be listed as a possible adverse effect in the product information for all statins.

Memory loss:
With the exception of rosuvastatin which had a higher incidence rate (3.0 cases per 1000 patient-years with rosuvastatin vs 0 cases with placebo), the incidence rates of memory loss with statin use compared to placebo were similar. Limited information was available regarding whether the memory loss is short or long term and the reversibility of the event.

The SPC for atorvastatin already includes memory loss (amnesia) as an adverse effect. For the remaining statins, although it was not possible to assess a true causality link (as there was insufficient information regarding confounding factors), post-marketing reported cases of positive rechallenge could not rule out the causality of statins in association with memory loss.
Therefore memory loss will be listed as a possible adverse effect in the product information for all statins.

Micturition disorders:
A review of the literature did not identify events of micturition disorder related to statin therapy, and similar incidence rates of micturition disorders have been reported for statins and placebo in clinical trials and reported cases.

The SPC for pravastatin already contains information on abnormal urination (including dysuria, frequency, and nocturia) as an adverse effect. On the basis of the assessments in the review, it was not considered necessary to list micturition disorders in the SPCs for the remaining statins, as the evidence for an association of micturition disorders with their use was weak; However this adverse effect will continue to be closely monitored.

Sexual disturbance:
A review of the literature suggested a possible causal relationship between statin use and sexual dysfunction.

The SPCs for atorvastatin and pravastatin already list sexual dysfunction as a possible adverse effect, as previous reviews have concluded that a causal association is possible. From this assessment it was considered prudent to include sexual dysfunction in the SPCs for all statins, as the data suggest a class effect. Therefore, sexual dysfunction will be listed as a possible adverse effect in the product information for all statins.

Depression:
Incidence rates of depression with statin use compared to placebo were similar in clinical trials, apart from a study that compared atorvastatin with pravastatin[57].Limited information was available regarding dose. Lovastatin and rosuvastatin demonstrated a possible dose relationship, with a higher reporting rate for the 40mg dose.

Based on the data provided, amendment of the SPC to include depression appeared warranted for atorvastatin and rosuvastatin. For the remaining statins it was not possible to assess a true causality link, as the data was limited by insufficient information on confounding factors. However, although review of the literature did not provide a direct link between statin use and depression, a study suggested that depression may be related to low levels of cholesterol[55]. Therefore, depression will be listed as a possible adverse effect in the product information for all statins.

Interstitial pneumopathy:
A causal relationship between the individual statins and interstitial pneumopathy is difficult to establish because of limited data. There has been no evidence of a positive rechallenge being reported. However, data from published literature on statins suggest the possibility of a class effect with relation to hypersensitivity pneumonitis or non-specific interstitial pneumonia[24, 25].
Balancing the potential differences between members of the statin class and the seriousness of this adverse event, a statement regarding interstitial pneumonitis as a potential adverse effect will be added to the product information for all individual statins. It is important to highlight the very rare possibility that interstitial lung disease may result from statin medication, as the reactions are potentially life-threatening.

Summary of conclusions
On the basis of the review described in this report, it was concluded that product information for all statins should be updated with warnings on the possible adverse events of sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease. The wording will be the same for all statins, and is given in detail in section 4.

4. CHANGES TO PRODUCT INFORMATION

Summary of Product Characteristics (SPC) warnings:

Section 4.4 – Special warnings and precautions for use

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Section 4.8 – Undesirable effects

The following adverse events have been reported with some statins:
• Sleep disturbances, including insomnia and nightmares [where this is not already listed]
• Memory loss
• Sexual dysfunction [where this is not already listed]
• Depression
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Patient Information Leaflet:

Check with your doctor or pharmacist before taking [statin] if you:

• Have severe respiratory failure

Possible side effects

• Sleep disturbances, including insomnia and nightmares
• Memory loss
• Sexual difficulties
• Depression
• Breathing problems including persistent cough and/or shortness of breath or fever

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6. GLOSSARY

Alveolitis
Inflammation of air sacs in the lung

Alzheimer's disease
A progressive form of **dementia** occurring in middle age or later

Antibiotics
Treatment for bacterial or fungal infections

Benign prostatic hyperplasia
Enlarged prostate gland

Bipolar disorder
A mental illness that causes repeated episodes of depression

Cardiovascular
Related to the heart and blood vessels

Case-control
A **clinical study** that compares one group of individuals with a disease or condition with another group of individuals who are free from that particular disease

Causality
Establishing that a factor or substance is definitely associated with the onset of a illness or medical condition

Cerebrovascular
Related to the blood vessels of the brain

Chemotherapeutic agents
Chemical substances used to treat or prevent disease (usually cancer)

Cholesterol
A fatty substance found in blood and body tissue; elevated levels of cholesterol are associated with fatty deposits on blood vessel walls and resultant cardiovascular problems

Chronic
Describes a disease of a long duration

Clinical study
A research study undertaken to test medicines in humans

Cognition
Mental processes involved in behaviour and acquiring knowledge

Confidence interval
A statistical range of numbers with a specific probability that a value lies within this range
Coronary
Related to the arteries of the heart

Corticosteroids
An anti-inflammatory substance produced naturally by the body, which is also available in synthetic form as a medicine

Creatinine phosphokinase
A substance involved in breaking down proteins in the body

Cross-over study
A clinical trial which tests a medicine in one group of volunteers against either an inactive treatment or a different medicine for comparison in another group. The groups exchange treatment after an agreed amount of time.

Cytotoxic
Causes damage to cells in the body

Dementia
Deterioration of intellect

Dermatomyositis
A condition characterised by weakness and swelling of muscles and skin

Diabetes mellitus
A condition in which the body does not produce enough insulin, or when insulin does not work properly. Insulin controls the level of sugar in the blood

Dosing regimen
The schedule detailing how much medicine should be given, and when

Double–blind study
A clinical trial in which the identity of the test medicine is hidden from both the volunteers and the study investigators (to remove any possible bias from the results)

Dyspnoea
Difficulty in breathing

Dysthymia
Mild depression

Dysuria
Painful or difficult urination

Eosinophilia
An increase in the number of white blood cells in the body, usually due to allergies or certain diseases

Fatigue
Mental or physical tiredness

Fibrate
A drug that reduces fats in the blood

Gynaecomastia
Enlargement of breasts in men, either due to a hormone imbalance or to certain drug treatments

Hypercholesterolaemia
Elevated levels of cholesterol in the blood

Hyperlipidaemic
Elevated levels of cholesterol or fatty acids (triglycerides) in the blood

Hypersensitivity pneumonitis
Inflammation of the lung caused by repeatedly breathing in foreign substances, such as dust

Hypertension
High blood pressure

Hypoglycaemia
Low blood sugar levels, which lead to muscular weakness and mental confusion

Incidence rates
The number of new episodes of an illness that occur in a population over a period of time

Incontinence
An involuntary (and inappropriate) release of urine

Innervation
The nerve supply to an area of the body or an organ

Interstitial pneumonia
Inflammation of lung tissue

Lower urinary tract
The organs of the body that produce and discharge urine

Lupus
A **chronic** inflammatory skin disease

Metabolism
The process of breaking down substances in the body to release energy for other process

Micturition
Urination

Mitochondrial
Related to the mitochondria (part of a cell)

Morphology
The different structures of living organisms

Mortality
The incidence of death in a population over a given period

Multiple sclerosis
A chronic disease of the nervous system

Neurogenic
Caused by disease or dysfunction of the nervous system

Neuronal
Related to nerves

Nocturia
The need to urinate at night

Oliguria
The production of an abnormally small amount of urine, which may be caused by kidney disease

Organising pneumonia
Unresolved **pneumonia**

Overactive bladder syndrome
A condition characterised by an urge to urinate, sometimes with accompanying incontinence

Over-the-counter medication
A drug that may be purchased directly from a pharmacy without a prescription

Oxygen free radicals
Reactive molecules containing oxygen that can cause cell damage

Patient-years
The total number of years that patients are in a clinical study, divided by the number of events that are being studied

Pathological
Related to, or arising from, disease

Phospholipases
A substance that breaks down lipids (containing a phosphate group) in the body

Physiological
Normal body function (not related to disease)

Placebo
Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Pneumonia
Inflammation of the lung caused by bacteria

Pneumonitis
Inflammation of the airspaces in the lung

Pollakuria
Abnormally frequent urination

Polymyositis
A disease of the muscles, causing them to be weak and inflamed

Positive dechallenge
A reduction in an adverse reaction after a drug is withdrawn

Positive rechallenge
A reappearance of an adverse reaction after a drug is re-administered (following its withdrawal)

Prevalence
A measure of the occurrence(s) of a particular disease or condition in a population over a given period

Primary prevention study
A study evaluating whether a particular disease or condition can be avoided by behaviour modification or treatment

Prospective cohort
A study in which a group of individuals are followed until the occurrence of the disease or condition being evaluated

Pulmonary
Related to the lung

Pulmonary fibrosis
A thickening and scarring of the airsacs in the lungs, causing progressive breathlessness

Radiology
A branch of medicine that uses imaging technology (eg, ultrasound) to diagnose disease

Randomised controlled trial
A **clinical trial** in which the study participants are randomly assigned to receive either the test medicine or a **placebo/**comparator medicine

Retrospective cohort
A study in which the history of a group of individuals with a particular disease or condition is examined

Somnolence
Sleepiness

Synthesis
The combination of elements or simple compounds to produce a new substance

Testosterone
The main male sex hormone

Tocopherol
Vitamin E

Transient global amnesia
Memory loss disorder experienced by middle-aged and elderly individuals

Urinary retention
Inability to pass urine from the bladder, usually due to an obstruction

Vasculitis
Inflammation of blood vessel walls

Voiding
Emptying the bladder, or urinating