Medicines & Healthcare products Regulatory Agency

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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In our first article, we advise on the introduction of a patient card for men taking finasteride. This will help raise awareness of the risk of psychiatric side effects and sexual dysfunction, including the potential for sexual dysfunction to persist after treatment has stopped.

Secondly, we remind healthcare professionals to be alert to the risk of neuropsychiatric reactions in patients when prescribing montelukast. Healthcare professionals should advise patients and their caregivers to be alert to these risks and to seek medical advice immediately if neuropsychiatric reactions occur.

Finally, we provide a summary of recent letters and notifications sent to healthcare professionals about medicines.

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Finasteride: reminder of the risk of psychiatric side effects and of sexual side effects (which may persist after discontinuation of treatment)

A patient alert card is being introduced for men taking finasteride to help raise awareness of the risk of psychiatric side effects and sexual dysfunction, including the potential for sexual dysfunction to persist after treatment has stopped. Healthcare professionals are reminded to monitor patients for both psychiatric and sexual side effects.

Advice for healthcare professionals:

- finasteride has been associated with depression, suicidal thoughts and sexual dysfunction
- patients have reported that sexual dysfunction (including decreased libido and erectile dysfunction) has persisted even after treatment was stopped
- before prescribing finasteride, ask patients if they have a history of depression or suicidal ideation
- advise patients to stop finasteride 1mg (Propecia) for male pattern hair loss immediately if they develop depression or suicidal thoughts and to contact their doctor as soon as possible
- advise patients prescribed finasteride 5mg (Proscar) for benign prostatic hyperplasia to consult their doctor for further medical advice as soon as possible if they develop depression or suicidal thoughts
- monitor patients for psychiatric and sexual side effects
- a patient card will be introduced in all finasteride packs, which will highlight the risk of sexual side effects and psychiatric side effects reported with finasteride to increase awareness among patients and prescribers
- report suspected adverse drug reactions associated with finasteride via the Yellow Card scheme

Advice for healthcare professionals to give to patients and carers:

- finasteride is a medicine that helps with the management of male pattern hair loss (androgenic alopecia; 1 milligram (mg) formulation) and benign (non-cancerous) enlargement of the prostate (benign prostatic hyperplasia; 5mg formulation)
- finasteride has been associated with depressed mood, depression, suicidal thoughts and sexual dysfunction (including decreased sex drive and erectile dysfunction)
- in some cases sexual dysfunction has persisted in patients even after they have stopped taking finasteride

- before taking finasteride, inform your doctor if you have any personal history of depression or suicidal thoughts
- stop finasteride 1mg (Propecia) immediately if you develop depression or suicidal thoughts and contact your doctor as soon as possible
- if you are prescribed finasteride 5mg (Proscar) and you develop depression or suicidal thoughts, you should contact your doctor for further medical advice as soon as possible
- if you experience any problems with sexual function such as inability to get and maintain an erection or decrease in sex drive, please discuss this with your prescriber or doctor
- you may not notice some changes in your mood and behaviour so it is very important to tell your friends and family that you are taking this medicine and that it can have effects on psychological well-being. Others may notice changes and help you quickly identify any symptoms that you need to talk to your doctor about
- always read the leaflet that is provided alongside your medicine, which contains information about taking finasteride and a full list of known possible side effects
- if you experience any side effects, please report them to the Yellow Card scheme

Review of persistent sexual dysfunction and psychiatric side effects with finasteride

Finasteride is a 5 alpha-reductase-type-2 inhibitor. The 1mg dose (Propecia) is indicated in men 18 to 41 years of age for the treatment of male pattern hair loss (androgenetic alopecia). The 5mg dose (Proscar) is indicated for the treatment and control of benign prostatic hyperplasia in adults.

The MHRA completed a safety review into finasteride following concerns from patients regarding a lack of awareness of psychiatric and sexual side effects amongst patients and healthcare professionals. We issued a previous in 2017, however at the time the potential for persistence of some of the side effects was not widely known.

The MHRA recently reviewed the available evidence, including Yellow Card reports, published scientific literature and actions by other regulators, and this was considered by the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines (CHM). The PEAG noted that the product information for finasteride contains information regarding the potential for persistent sexual side effects after discontinuation with finasteride and depression and suicidal ideation. However, these side effects are not well known by prescribers and patients and therefore a Drug Safety Update article was recommended.

The PEAG also recommended inclusion of a patient card inside the pack. The card aims to increase awareness of the side effects including depression, suicidal thoughts

and sexual dysfunction, and to advise patients on what to do if they experience these adverse effects. The patient card will be introduced this year.

A Public Assessment Report has been published on the risks associated with finasteride.

UK reports of persistent sexual dysfunction after discontinuation of finasteride

Since the first report received in November 1992, the MHRA has received 426 Yellow Card reports up until 5 April 2024 of finasteride (both 1mg and 5mg formulations) and sexual dysfunction, including reports of erectile dysfunction (inability to get and maintain an erection) and decreased sex drive. In almost half of these reports, the outcome was recorded as ‘not recovered’ or ‘not resolved’.

UK reports of psychiatric dysfunction with finasteride

Since the first report received in February 1993, the MHRA has received 281 reports of finasteride and depressed mood disorders and suicidal and self-injurious behaviours, up until 5 April 2024.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to finasteride via the Yellow Card scheme. Your report will help us safeguard public health. Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, treatment dates and particularly if a side effect continued or started after treatment was stopped.

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Montelukast: Reminder of the risk of neuropsychiatric reactions

Healthcare professionals prescribing montelukast should be alert to the risk of neuropsychiatric reactions in all patients including children and adolescents. Reported neuropsychiatric reactions include sleep disorders, hallucinations, anxiety and depression, as well as changes in behaviour and mood. Healthcare professionals should advise patients and their caregivers to be alert to these risks and seek medical advice as soon as possible if neuropsychiatric reactions occur.

Advice for healthcare professionals:

- the warnings in the Patient Information Leaflet and Summary of Product Characteristics for all montelukast products in the UK have been strengthened and highlighted with a black box for greater emphasis
- be alert for neuropsychiatric reactions in patients taking montelukast; events have been reported in adults, adolescents, and children
- discontinue montelukast if patients experience new or worsening symptoms of neuropsychiatric reactions
- advise patients and their caregivers to carefully read the list of neuropsychiatric reactions in the Patient Information Leaflet and to seek medical advice immediately should they occur
- report suspected adverse drug reactions associated with montelukast on a Yellow Card

Advice for healthcare professionals to provide to patients:

- infrequently, some patients may experience new or worsening changes in mood, sleep or behaviour such as nightmares, aggression, anxiety or thoughts about self-injury while using montelukast
- you should seek immediate medical attention if you or your child experiences these symptoms; your prescriber is best placed to advise you on stopping this medicine if needed
- it is very important to tell your friends and family that you are taking montelukast and that this medicine is associated with infrequent neuropsychiatric side effects. This is because you may not notice some changes in your mood, sleep and behaviour. Other people may notice changes or new symptoms that you need to talk to your prescriber about
- the Patient Information Leaflet that comes with all montelukast products now includes warnings and advice about these psychiatric side effects in a black box

- it is important to read the Patient Information Leaflet that comes with your medicine or your child's medicine
- talk to a healthcare professional if you or your child are experiencing any problems with the medicine

  patients, parents, and caregivers can report suspected adverse drug reactions to montelukast via the Yellow Card scheme

Review of neuropsychiatric reactions with montelukast

To increase awareness of the risks of neuropsychiatric effects with montelukast, new boxed warnings will be introduced to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) to make these risks more prominent to the reader. These warnings have been updated with the current evidence on the risk. Healthcare professionals and patients should familiarise themselves with this information.

It is well established that neuropsychiatric reactions may infrequently occur in association with montelukast. These are documented in the SmPC and PIL of all marketed montelukast products in the UK. A Drug Safety Update was published in September 2019 to remind healthcare professionals and patients of the risk of neuropsychiatric reactions with montelukast.

Since these actions were implemented, the MHRA has continued to receive Yellow Card reports and queries from patients and caregivers. The MHRA has therefore conducted a further review to evaluate the new evidence, taking into consideration the experiences of patients and caregivers and independent clinical advice from paediatricians, specialists in mental health and respiratory health, as well as experts in medicines safety at Expert Advisory Groups of the Commission on Human Medicines.

Review of the Yellow Card data has indicated a potential lack of awareness of the risk of neuropsychiatric reactions with montelukast amongst healthcare professionals, patients and their caregivers. Based on the overall evidence, the Pharmacovigilance Expert Advisory Group (PEAG) advised that montelukast should be immediately withdrawn due to the nature of the neuropsychiatric reactions, and that immediate withdrawal may help prevent escalation to more serious events. Therefore, updates to the product information have been implemented to ensure patients and healthcare professionals are aware of these risks and what action should be taken.

UK reports of neuropsychiatric reactions with montelukast

A range of neuropsychiatric reactions have been reported in association with montelukast. Among these are:

- sleep disturbances, depression and agitation including aggressive behaviour (may affect up to 1 in 100 people taking montelukast)
- disturbances of attention or memory (up to 1 in 1,000 people)

- very rarely, hallucinations and suicidal thinking and behaviour (up to 1 in 10,000 people).

See the SmPC (section 4.8) and the PIL (section 4) for full details.

Since first authorised in the UK in 1998, there have been approximately 44 million prescriptions of montelukast issued. During this time, the MHRA has received 1,223 reports of suspected neuropsychiatric adverse reactions. Information on neuropsychiatric reactions with montelukast was first introduced in the SmPC in 2008 and a detailed warning was added in 2019.

Of these, the most frequently reported suspected neuropsychiatric reactions associated with montelukast for all age groups were sleep disorders, hallucinations, anxiety and depression, as well as changes in behaviour and mood. The most frequently reported reactions in younger children (up to and including 12 years old) were aggression, nightmares and anxiety while in older children (13 years old up to and including 17 years old) the most commonly reported were anxiety, suicidal ideation and depression.

About montelukast

Montelukast sodium is an oral leukotriene receptor antagonist. It is indicated for patients 6 months and older:

- for the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting beta-agonists provide inadequate clinical control of asthma
- for the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

Report any suspected adverse reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme. Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

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Letters and medicine recalls sent to healthcare professionals in March 2024

Letters

In March 2024, the following letters were sent or provided to relevant healthcare professionals:

- Fiasp® FlexTouch® (fast-acting insulin aspart) 100 units/ml solution for injection 3ml pre-filled pen: Supply Shortage in the UK
- Oestrogel (estradiol) Pump-Pack 750 micrograms/actuation Gel Recall VERORAB, powder and solvent for suspension for injection - PLGB 46602/0029
- Diazepam Desitin 10mg Rectal Solution BSV
- GAVRETO®▼(pralsetinib): Planned transition of Market Authorisation Holder for GAVRETO®▼(pralsetinib) from Roche Products Ltd to BluePrint Medicines resulting in discontinuation of supply from Roche Products Ltd
- Tresiba® FlexTouch® 100 U/mL solution for injection (insulin degludec): Supply Shortage in the UK and Tresiba® FlexTouch® 200 U/mL solution for injection (insulin degludec): Medication error
- Norditropin NordiFlex® (somatropin): Product Discontinuation Norditropin® FlexPro® 5mg/1.5ml (somatropin): Drug Shortage and Pause in production

Medicine Recalls and Notifications

In March 2024, recalls and notifications for medicines were issued on:

Class 2 Medicines Recall: medac GmbH (t/a medac Pharma LLP), Sodiofolin 50 mg/ml, solution for injection/infusion (folinic acid 400mg/8ml vial), EL(24)A/08. Issued: 12 March 2024. medac GmbH (t/a medac Pharma LLP) is recalling the product for the batch specified in this notification due to particles detected during long-term stability tests.

Class 3 Medicines Recall: Besins Healthcare (UK) Ltd, Oestrogel Pump-Pack 750 micrograms/actuation Gel (estradiol), EL (24)A/09. Issued: 19 March 2024. Besins Healthcare (UK) Ltd has informed the MHRA that a defective pump system was detected in two batches of Oestrogel Pump-Pack 750 micrograms/actuation Gel.

Class 4 Medicines Notification: Fresenius Kabi Limited, Sodium Chloride Intravenous Infusion 0.9% Freeflex, EL (24)A/10. Issued: 21 March 2024. Fresenius Kabi Limited has informed the MHRA of an error on the infusion bag packaged into the specific batches of Sodium Chloride Intravenous Infusion 0.9% Freeflex.

Medical Device Safety Information

We recently published Device Safety Information pages on the following topics:

Counterfeits and unbranded copies of LifeVac anti-choking devices may fail to work correctly or worsen choking incidents if used, (DSI/2024/003). Issued: 25 March 2024. Anti-choking devices are intended to alleviate choking incidents after Basic Life Support protocols have been attempted and failed. There are numerous counterfeit and unbranded anti-choking devices being sold in the UK online which do not have a valid UKCA or CE mark and may pose a significant risk of worsening choking if used. These

devices should not be used in the event of a choking emergency and should be disposed of once identified as counterfeit or non-compliant. For additional information, please refer to the Device Safety Information page.

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