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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This month, we announce that oral lidocaine-containing products for infant teething are only to be available under the supervision of a pharmacist so that parents and caregivers can receive guidance about managing infant teething symptoms (page 2).

In our second article, read important updates on compliance with pregnancy prevention measures for valproate medicines (page 4) and ask if you are acting in full compliance with these new strengthened measures. Although use of valproate in female patients is slowly declining, wide geographical variation exists in prescribing rates across UK – we encourage you to check the latest data for your region. Importantly, women continue to report instances when they have not received the patient information with their dispensed valproate medicine. Read a reminder of responsibilities and guidance available on page 4.

In our third article, we communicate new information about risk of severe and fatal burns with paraffin-containing and paraffin-free emollients. Advise patients who use these products not to smoke or go near naked flames, and warn about the easy ignition of clothing, bedding, dressings, and other fabric that have dried residue of an emollient product on them (page 9).

In our fourth article, we advise you that glucose levels should be monitored closely in patients with diabetes during direct-acting antiviral therapy for chronic hepatitis C, particularly within the first 3 months of treatment (page 11). Patients with diabetes may experience symptomatic hypoglycaemia if diabetes treatment is continued at the same dose due to potential for an enhanced hypoglycaemic effect. Modify diabetes medication or dose when necessary.

Next, on page 13, we issue warnings that off-label use of muco-adhesive buccal tablets for adrenal replacement therapy in children could result in insufficient cortisol absorption and, in stress situations, life-threatening adrenal crisis.

Finally, read our monthly highlight page of letters and alerts to healthcare professionals on pages 14 and 15, including actions regarding the pharmacy-level recall of some valsartan medicines.

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Oral lidocaine-containing products for infant teething: only to be available under the supervision of a pharmacist

Oral lidocaine-containing products for infant teething are only to be available under the supervision of a pharmacist so that parents and caregivers can receive guidance about managing infant teething symptoms. Non-medicinal options such as a teething ring or massaging the gum should be the first line for relieving infant teething symptoms, and lidocaine-containing products should only be used when simple measures have failed to provide sufficient relief.

Advice for healthcare professionals:

- all oral lidocaine-containing products with an infant teething indication are becoming pharmacy medicines; newly manufactured products with updated instructions will be available only in pharmacies where advice on their correct use and on babies' health can be given – see Quick reference guide for pharmacists
- pharmacists should only recommend use of these products when local non-medicinal treatments such as a teething ring or massaging the gum have failed to provide sufficient relief
- if oral lidocaine-containing products are to be used, remind parents and caregivers to read the advice in the Patient Information Leaflet carefully, especially for dose and administration, and to seek medical attention if their child's condition does not improve
- advise parents and caregivers that other lidocaine products authorised in adults or for other conditions such as mouth ulcers should not be used for treatment of infant teething pain
- sugar-free paracetamol or ibuprofen suspensions, administered according to the approved indication and dose for weight and age, may also be considered for the relief of teething symptoms
- report any suspected adverse drug reactions to lidocaine products via the Yellow Card Scheme

Review of oral lidocaine-containing teething products

This article was published online on 13 December 2018, in advance of the rest of the December 2018 Drug Safety Update. This was to enable healthcare professionals and the public to receive consistent information on advice for lidocaine products for teething.

The Commission on Human Medicines (CHM) has advised on measures to improve the safe use of lidocaine-containing products for teething in children. In an in-depth review of the benefits and risks of these products, CHM identified a number of reports of medication error received via the Yellow Card Scheme (see Public Assessment Report). Most reports did not include an associated adverse event and were not thought to result in harm, but the committee recommended that the administration instructions should be improved and harmonised to ensure parents and caregivers received consistent advice on the safe use of these medicines in babies.

CHM recommended that pharmacists were best placed to provide guidance to parents and caregivers on options for teething symptoms, including when symptoms could suggest more serious conditions that need medical assessment.

New measures: access to healthcare professional advice and new warnings and instructions

The legal status of newly manufactured stock of oral lidocaine-containing products indicated for infant teething is changing from general sale (GSL) to pharmacy (P).

This change means that oral lidocaine products for infant teething can only be sold in pharmacies where advice can be given by the pharmacist (see also Quick reference guide for pharmacists). Instructions for administration and safety warnings are being updated in the new Patient Information Leaflet. Advice is being given to parents and caregivers to seek medical attention if their child's condition does not improve and not to use more than one product containing lidocaine at the same time. We have produced a parent and caregiver information sheet (large print version available) to help you discuss the new advice.

Oral lidocaine products that are approved in adults or in other conditions (eg, mouth ulcers) will remain GSL but should not be used in infants for teething because they have different approved dosing regimens. The Patient Information Leaflets and cartons of these oral lidocaine-containing products without a teething indication are being updated accordingly.

General advice about teething

Teething is a normal process, usually beginning at around 6 months of age. NICE recommends simple, self-care measures as first steps for relief of associated discomfort. These include gentle rubbing of the gum with a clean finger and allowing the child to bite on a clean and cool object. Pharmacists should advise parents and carers to only use oral lidocaine products when these non-medicinal methods do not provide necessary relief.

Sugar-free paracetamol or ibuprofen suspensions, administered according to the approved indication and dose for weight and age, can also be considered for the relief of teething symptoms.

Availability of updated medicines and advice

Updated oral lidocaine-containing products will be available in pharmacies from the beginning of 2019. Products with older packaging are no longer being manufactured. Pharmacists should provide parents and caregivers with the most up-to-date instructions (provided in Quick reference guide for pharmacists or in Patient Information Leaflets on eMC), including with any last remaining GSL packs during the transition.

Report suspected adverse drug reactions

Suspected adverse drug reactions to oral lidocaine-containing products should be reported via the Yellow Card Scheme, including medication error resulting in harm. For more information about why it is important to report Yellow Cards in babies and children and how you can support this further, see article in November 2018 Drug Safety Update.

Further information

- MHRA parent and caregiver information sheet
- MHRA Press release
- MHRA Public Assessment Report
- Quick reference guide for pharmacists

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 1.

Valproate medicines: are you in acting in compliance with the pregnancy prevention measures?

Although use of valproate medicines in female patients continues to slowly decline, there is wide variation in prescribing between Clinical Commissioning Groups (CCGs). Women continue to report instances when they have not received patient information with their dispensed valproate medicine. All healthcare professionals must continue to identify and review all female patients on valproate, including when it is used outside the licensed indications (off-label use) and provide them with the patient information materials every time they attend their appointments or receive their medicines (including the Patient Information Leaflet at dispensing).

New information

1. Compliance by healthcare professionals with the new valproate measures for pregnancy prevention appears currently patchy
2. Women are not always receiving Patient Information Leaflets with their medicines, as is required
3. Some women using valproate for off-label indications are not being reviewed in line with the new pregnancy prevention measures
4. Guidance is available for psychiatrists on the withdrawal of, and alternatives to, valproate in women of childbearing potential

Advice and information for healthcare professionals:

- valproate should not be used in women and girls of childbearing potential unless there is no suitable alternative and the conditions of the Pregnancy Prevention Programme are met
- although use in female patients in the UK continues to slowly decline, data shows a wide geographical variation in the prescribing of valproate medicines – you can check your region here
- women continue to report instances when pharmacists have not provided a Patient Information Leaflet or a Patient Card when dispensing valproate
- ensure you are complying with the responsibilities of healthcare professionals involved in the care of female patients on valproate – including when valproate is used outside the licensed indications (see advice on off-label use below)
- an audit function is available on all GP software systems – use this now to identify and recall all women and girls on valproate who may be of childbearing potential and refer to an appropriate specialist for a review

Reminder for pharmacists:

- always provide the statutory Patient Information Leaflet to female patients with a valproate medicine, even when dispensed in a pharmacy 'white dispensing box' (plain carton)
- remind women of the risks and provide with a Patient Card **every time** they are dispensed a valproate medicine – situations can change and a one-time conversation is not sufficient
- check whether women are enrolled in the Pregnancy Prevention Programme and have signed a Risk Acknowledgement Form – if not, dispense the prescription and advise the patient to speak to her GP as soon as possible (including by contacting the GP directly if necessary) for a specialist referral
- GPhC inspectors will be systematically checking compliance with the Pregnancy Prevention Programme during inspections of registered pharmacies (see GPhC statement)
- ensure materials are placed in a defined area in the pharmacy and that all staff, including locums, know where they are located and aware of the local policies
- if you require more copies, contact the Sanofi medical information department without delay on 0845 372 7101 or email UK-Medicalinformation@sanofi.com

Valproate Pregnancy Prevention requirements, including when used off-label

Valproate should not be used in girls (of any age) and women of childbearing potential unless there is no suitable alternative, as judged by a specialist experienced in the management of epilepsy or bipolar disorder. If valproate is the only effective or tolerated medicine, women and girls of childbearing potential should be enrolled in the Pregnancy Prevention Programme and a Risk Acknowledgement Form should be completed by the prescriber and patient every year at an annual specialist review (see Drug Safety Update April 2018 and Drug Safety Update May 2018).

We are aware of off-label use of valproate for pain, migraine, and other conditions. Prescribers are reminded that off-label use of valproate carries all the accompanying responsibilities for the pregnancy prevention measures to be followed (see guidance from MHRA and the General Medical Council on prescribing unlicensed medicines).

Irrespective of condition being treated, valproate medicines should not be used in women of childbearing potential unless the patient is fully aware of the serious risks in pregnancy and the conditions of the Pregnancy Prevention Programme are fulfilled. Valproate should only be initiated in girls (of any age) and women of childbearing potential by specialists experienced in the management of their treated condition. The Risk Acknowledgement Form should be completed by the specialist prescriber at initiation. If valproate treatment is to be issued by repeat prescription in general practice, the GP and specialist should ensure the patient has an annual review with a specialist prescriber to discuss the need for treatment and any change in her situation. If valproate treatment is continued, the risks and pregnancy prevention measures must be fully discussed with the patient, and the Risk Acknowledgement Form completed by both prescriber and patient annually.

For patients with a first language that is not English, the conclusions of the EU review and a summary of the new measures are available on the website of the European Medicines Agency in 22 European languages, including Polish.

New guidance for prescribers

A Position Statement from the Royal College of Psychiatrists is now available to provide guidance for prescribers on the withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness. The guidance summarises evidence for alternatives to valproate, provides advice on how women who are currently undergoing treatment with valproate medicines can be switched to alternative treatments, and provides a link to the recommended annual risk acknowledgment form to facilitate discussions with patients about hazards associated with valproate medicines.

Reports of instances of non-adherence to new regulatory measures and reminder to pharmacists

The MHRA has worked closely with stakeholders, including charities and patient support networks, to implement and monitor compliance with the 2018 strengthened regulatory measures to protect female patients taking valproate.

Concerns have been raised by support networks that patients are not being properly informed of the risks and that they have not been given the patient information materials including with every dispensed medicine. In a survey of 78 patients on the INFACT website between June and September 2018, 88% respondents had not signed the Risk Acknowledgment Form to agree they had been informed of the risks of valproate in pregnancy.

Many respondents to the survey had also received their valproate medicines in a white dispensing boxes (plain cartons) without the statutory Patient Information Leaflet (58% of respondents stated that they never receive a leaflet if their medicines are repackaged in a white dispensing box). Only 8% of respondents had ever received the new Patient Card from their pharmacist with their valproate medicine.

Given the serious risk of harm with valproate being used in pregnancy, with up to 40% of exposed children having a birth defect or persistently impaired mental development, the Patient Information Leaflet should always be provided with this medicine, even when dispensed in a white dispensing box. Warning stickers should also be applied to white dispensing boxes to ensure all patients are visually reminded of the risk.

If pharmacists or pharmacies require additional Patient Information Leaflets, they may photocopy the leaflet from the bulk product or download them from the following sites, together with the risk materials:

- MHRA https://www.gov.uk/guidance/valproate-use-by-women-and-girls
- eMC https://www.medicines.org.uk/emc/
- Sanofi http://www.sanofi.co.uk/l/gb/en/layout.jsp?scat=7CF435AE-4B79-4FDE-837B-3AFA25D76B2F

For hard copies of all the information contact Sanofi medical information department on 0845 372 7101 or email UK-Medicalinformation@sanofi.com.

The MHRA is working with the wider healthcare system, including professional regulators, to ensure compliance with the new regulatory measures. When inspecting registered pharmacies, inspectors from the General Pharmaceutical Council are looking to see whether the standards are being met, and will systematically check compliance with the requirements of the Pregnancy Prevention Programme (see statement from GPhC).

See also the joint resource for pharmacists on Valproate Safety from the Community Pharmacy Patient Safety Group and Royal Pharmaceutical Society to support pharmacy teams in helping women and girls who have been prescribed valproate medicines. The resource includes a decision pathway and key points for consideration to prompt conversations between the pharmacy team and their patients.

Analysis of prescribing data and trends, including for CCGs

We have recently completed analysis of primary care prescribing data for valproate medicines from the Clinical Practice Research Datalink (CPRD) up to the end of June 2018. For the detailed data, see CPRD Study Monitoring the Use of Valproate in Girls and Women in the UK: January 2010 to June 2018.

There continues to be a slow, sustained decline in the initiations of valproate medicines in female patients, particularly in adolescent girls. Overall rates of prescribing of valproate in female patients in primary care are also slowly declining throughout the UK. However, there were an estimated 3.3 per 10,000 pregnancies in the UK exposed to the harm of valproate in 2017 – around 250 live births.

Data from the NHS in England shows clear variation in the prescribing of valproate in women of childbearing age across England. You can review the data from your CCG from the NHS Business Services Authority, including how prescribing has changed over time and how it compares to neighbouring CCGs.

We will continue to monitor these and other data sources, including clinical audits and patient surveys. We will communicate updates via Drug Safety Update and the Valproate Guidance page. If data show women continue to be exposed to valproate during pregnancy and therefore measures may have not been sufficient to inform and protect women and their children, MHRA will consider the need for strengthened action.

About the data used to assess prescribing

As part of their responsibility for the safety of medicines, the MHRA monitors data on the impact of regulatory action. The MHRA uses a variety of data sources for this.

CPRD collects de-identified patient data from a network of GP practices across the UK. Primary care data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset. The data used here includes over 2.2 million currently registered patients.

Data for CCGs in England is from the NHS Business Services Authority (NHSBSA). Quarterly data for based on the number of female patients of childbearing age who have received prescriptions for sodium valproate (including valproic acid and semisodium valproate). At the time of publication, data are available up to September 2018.

Background

Valproate medicines are licensed for the treatment of epilepsy and bipolar disorder. Epilim▼ and Depakote▼ are the most commonly dispensed valproate medicines in the UK. Other brands available are Convulex▼, Episenta▼, Epival▼, Kentlim▼, Orlept▼, Syonell▼, and Valpal▼.

Valproate is highly teratogenic and use in pregnancy leads to physical birth defects in 10 in every 100 babies (compared with a background rate of 2 to 3 in 100) and persistent neurodevelopmental disorders in approximately 30 to 40 in every 100 children born to mothers taking valproate.

You can read more about the risk, and the actions taken to prevent exposure in pregnancy, in Drug Safety Update July 2018 and Drug Safety Update November 2018.

Ensure you are subscribed to receive Drug Safety Update or download the Yellow Card App to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Download the app via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 2.

Emollients: new information about risk of severe and fatal burns with paraffin-containing and paraffin-free emollients

Warnings about the risk of severe and fatal burns are being extended to all paraffin-based emollients regardless of paraffin concentration. Data suggest there is also a risk for paraffin-free emollients. Advise patients who use these products not to smoke or go near naked flames, and warn about the easy ignition of clothing, bedding, dressings, and other fabric that have dried residue of an emollient product on them.

Advice for healthcare professionals:

- emollients are an important and effective treatment for chronic dry skin conditions and people should continue to use these products. However, you must ensure patients and their carers understand the fire risk associated with the build-up of residue on clothing and bedding and can take action to minimise the risk
- when prescribing, recommending, dispensing, selling, or applying emollient products to patients, instruct them not to smoke or go near naked flames because clothing or fabric such as bedding or bandages that have been in contact with an emollient or emollient-treated skin can rapidly ignite
- there is a fire risk with all paraffin-containing emollients, regardless of paraffin concentration, and it also cannot be excluded with paraffin-free emollients. A similar risk may apply for other products which are applied to the skin over large body areas, or in large volumes for repeated use for more than a few days
- be aware that washing clothing or fabric at a high temperature may reduce emollient build-up but not totally remove it
- warnings, including an alert symbol, are being added to packaging to provide a visual reminder to patients and those caring for them about the fire hazard
- report any fire incidents with emollients or other skin care products to the Yellow Card Scheme

Risk of severe and fatal burns with emollients

The risk of severe and fatal burns with emollients containing more than 50% paraffins was communicated in January 2008 and April 2016 via Drug Safety Update, in addition to the National Patient Safety Agency alert in 2007.

Evaluation of more recently available data showed that products containing less than 50% paraffins have been associated with fatal burns and paraffin-free products also have a fire accelerant effect in tests when emollient residue builds up on fabric and the fabric is ignited.It is difficult to estimate the true size of the risk based on case reports because of the likely under reporting of such events. We are currently aware of 11 cases (5 Coroner's Regulation 28 reports to Prevent Future Deaths and 6 others) in which paraffin-based emollients are suspected to have contributed to the speed and intensity of a fire, resulting in fatal burns injury. There are also 50 fire incidents (49 fatal) reported by Fire and Rescue Services across the UK between 2000 and November 2018, in which emollients were known to have been used by the victim or were present at the fire premises. However, in most of these it is not clear what the attributable role of

paraffin creams in the deaths would have been, in the presence of multiple risk factors for a fire incident.

Mechanism of the risk

The emollient products are not flammable in, or of themselves. However, they act as an accelerant, increasing the speed of ignition and intensity of the fire when fabric with residue dried on it is ignited.

Review of new evidence

In response to the more recent evidence, MHRA convened an ad hoc Expert Group to advise the Commission on Human Medicines (CHM) on the benefits and risks of these products and the appropriate regulatory action to minimise risk and protect public health.

The CHM advised that, taking into account the very rare risk, the modifiable risk factors, and their important therapeutic role, the benefits of these products outweigh the risk. However, CHM advised that the following was needed to protect public health:

- outer packaging and product containers should include a warning about the fire hazard, with the advice not to smoke or go near naked flames

- where available, the Patient Information Leaflet or Instructions for Use and the Summary of Product Characteristics should be updated to include warnings about the risk and how best to minimise it

Additionally, MHRA is setting up a specific stakeholder group to make proposals for measures to promote education and awareness of this risk.

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 3.

Direct-acting antivirals for chronic hepatitis C: risk of hypoglycaemia in patients with diabetes

Monitor glucose levels closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C, particularly within the first 3 months of treatment, and modify diabetes medication or doses when necessary. Patients with diabetes may experience symptomatic hypoglycaemia if diabetic treatment is continued at the same dose due to potential for an enhanced hypoglycaemic effect.

Advice for healthcare professionals:

- rapid reduction in hepatitis C viral load during direct-acting antiviral therapy for hepatitis C may lead to improvements in glucose metabolism in patients with diabetes, potentially resulting in symptomatic hypoglycaemia if diabetic treatment is continued at the same dose
- be vigilant for changes in glucose tolerance and advise patients of the risk of hypoglycaemia during direct-acting antiviral therapy, particularly within the first 3 months when the viral load is being reduced, and modify diabetic medication or doses when necessary
- physicians who initiate direct-acting antiviral therapy in patients with diabetes should inform the healthcare professional in charge of the diabetic care of the patient
- report any suspected adverse drug reactions associated with direct-acting antiviral therapies to the Yellow Card Scheme without delay

Evidence for hypoglycaemia during direct-acting antiviral therapy

Studies[1,2,3,4,5,6,7] show that some patients with diabetes initiating direct-acting antiviral therapy for hepatitis C have experienced hypoglycaemia. The studies indicate that achieving sustained virological response (SVR) is associated with improvements in glycaemic control, compared to patients who relapse or are non-responders. Many studies recorded these changes in glycaemic control in the first 3 months of treatment. Some studies reported the need to adjust patient's diabetic medication following changes in glucose metabolism, with up to 30% of patients requiring adjustments to their treatment.

An EU review confirmed the risk of hypoglycaemia in patients with diabetes who had been initiated on direct-acting antivirals for chronic hepatitis C. Information on the risk is being added to the Summary of Product Characteristics and Patient Information Leaflet for these medicines.

Patients with diabetes should be closely monitored for changes in glucose levels, particularly in the first 3 months of treatment, and adjustments to their diabetic medication or doses made where necessary.

Background

Direct-acting antivirals for chronic hepatitis C infection include: daclatasvir (Daklinza▼); sofosbuvir/velpatasvir (Epclusa▼); ledipasvir/sofosbuvir (Harvoni▼); sofosbuvir (Sovaldi▼); sofosbuvir/velpatasvir/voxilaprevir (Vosevi▼); dasabuvir (Exviera▼); ombitasvir/paritaprevir/ritonavir (Viekirax▼); glecaprevir/pibrentasvir (Maviret▼); and elbasvir/grazoprevir (Zepatier▼).

Report any suspected adverse drug reactions

Any suspected adverse drug reactions to direct-acting antivirals should be reported to us on a Yellow Card. Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card app.

Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

You can also use the app to access the latest safety information from MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

Further information

PRAC recommendations on signals adopted at the 1-4 October 2018 PRAC meeting.

References

1. Ciancio A, et al. Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. *J Med Virol* 2018; 90: 320–27.

2. Hum J, et al. Improvement in Glycemic Control of Type 2 Diabetes After Successful Treatment of Hepatitis C Virus. *Diabetes Care* 2017; **40:** 1173–80.

3. Pavone P, et al. Improving of Glycaemic Control Associated with DAAs HCV Treatment Persists at SVR12. HIV Drug Therapy conference; Glasgow, UK; 28–31 October 2016. Poster P273.

4. Dawood AA, et al. Factors Associated with Improved Glycemic Control by Direct-Acting Antiviral Agent Treatment in Egyptian Type 2 Diabetes Mellitus Patients with Chronic Hepatitis C Genotype 4. *Diabetes Metab J* 2017; 41: 316–31.

5. Lyman A, et al. The Impact of Achieving Virologic Response from Hepatitis C Direct-Acting Antivirals on Diabetes Control. 2016 Fall Meeting of the Ohio College of Clinical Pharmacy (OCCP). Cleveland, OH, USA; 18 November 2016. Abstract 53.

6. Benitez-Gutierrez LM, et al. Rapid drop in serum glucose and hypoglycemia in chronic hepatitis C patients with diabetes during oral HCV therapy. AASLD 2016: The Liver Meeting; San Francisco, CA, USA; 13–17 November 2015. Abstract 1180.

7. LeClerc SB, et al. Viral response to hepatitis C direct-acting antivirals significantly improves diabetes control. AASLD 2016: The Liver Conference; Boston, MA, USA; 11–15 November 2016. Abstract 964.

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 4.

Hydrocortisone muco-adhesive buccal tablets: should not be used off-label for adrenal insufficiency in children due to serious risks

Risk of insufficient cortisol absorption and life-threatening adrenal crisis if muco-adhesive buccal tablets are used as adrenal replacement therapy.

Advice for healthcare professionals

- hydrocortisone muco-adhesive buccal tablets are indicated only for local use in the mouth for aphthous ulceration and should not be used for treating adrenal insufficiency
- substitution of licensed oral formulations of hydrocortisone with muco-adhesive buccal tablets can result in insufficient cortisol absorption and, in stress situations, life-threatening adrenal crisis
- prescribers and pharmacists should only consider use of licensed hydrocortisone products for adrenal replacement therapy
- report suspected adverse drug reactions, including medication errors resulting in harm, on a Yellow Card

Reports of off-label use in the UK

We have received Yellow Card reports of off-label use of hydrocortisone muco-adhesive buccal tablets for adrenal insufficiency in children in the UK. The reports raised concerns about possible aggravation of congenital adrenal hyperplasia following substitution with muco-adhesive buccal tablets.

Hydrocortisone muco-adhesive buccal tablets are indicated only for local use in the mouth for aphthous ulceration (mouth ulcers). The efficacy and safety of hydrocortisone buccal tablets to treat adrenal insufficiency have not been established. Suspected adverse event reports indicate that the buccal hydrocortisone tablets provide decreased cortisol release compared with conventional oral tablets. If muco-adhesive buccal tablets are prescribed as a substitute for adrenal replacement therapy, there is the risk of insufficient cortisol release and, in stress situations, life-threatening adrenal crisis.

There are oral formulations of hydrocortisone authorised for the treatment of adrenal insufficiency. Prescribers and pharmacists should only use of these licensed hydrocortisone products for this condition.

The product information of the hydrocortisone muco-adhesive buccal tablets is being updated with warnings about the serious risks associated with off-label use for the treatment of adrenal insufficiency.

Report suspected adverse drug reactions on a Yellow Card

Suspected adverse drug reactions to hydrocortisone should be reported to the Yellow Card Scheme, including those that may be related to off-label use or medication error resulting in harm. Please don't assume someone else will report an adverse drug reaction you witness – if in doubt report a Yellow Card.

For more about how you can support the Yellow Card Scheme in improving the safety of medicines in children, see November 2018 Drug Safety Update.

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 5.

Letters and drug alerts sent to healthcare professionals in November 2018

Letters

In November 2018, the following letters were sent to healthcare professionals:

- Supply of Standard Export pack of Quadrivalent Influenza Vaccine (split virion, inactivated) suspension for injection in a prefilled syringe PL 46602/0017 - Lot R3K781V, Expiry 31/08/2019
- Systemic and inhaled fluoroquinolones: risk of aortic aneurysm and dissection

Drug alerts and recalls

In November 2018, MHRA issued the following Alerts and recalls for drugs:

- Mitomycin-C Kyowa: Company-led Drug Alert. Issued 12 November 2018. Batch Number 6058517 is being recalled because an out-of-specification result for sub-visible particles was recorded at the 39-month time-point.
- Class 2 Medicines Recall: Teva UK Limited and Mylan - recall of some Valsartan containing products. Issued 30 November 2018 – see below for more.

Recall of some valsartan-containing products

You should also be aware of a European-level recall from pharmacies of certain batches of Teva valsartan-containing products and all unexpired Mylan valsartan-containing products as a precautionary measure due to possible contamination with NDEA. See the recall notice on the MHRA website (issued 30 November 2018).

Advice for healthcare professionals:

- stop supplying the affected products/batches listed immediately; quarantine all remaining stock and return it to your supplier using your supplier's approved process
- advise patients not to stop taking their medication as the risk of discontinuing the medicine is higher than the potential risk presented by the contaminant. A treatment review is not necessary until the next routine appointment.
- although shortages of valsartan-containing products are not anticipated, there may be some local supply issues – should this be the case, patients should be advised to speak to their doctor to discuss alternative treatments

This is a developing issue and the MHRA is actively involved with the European Medicines Agency and with other medicines regulators to determine any possible impact. An investigation into other potentially impacted products is continuing and further updates will be provided as the investigation progresses. Subscribe to MHRA drug alerts for updates.

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 6.

Medical Device Alerts issued in November 2018

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

The following alerts were recently issued:

- Suction catheters, gastro-enteral tubes, intermittent urology catheters and sterile urine drainage bags – potential breach in sterile barrier packaging (MDA/2018/034). Issued 14 November 2018. Manufactured by ConvaTec Limited – use of affected devices may increase risk of patients getting infections.

- All T34 ambulatory syringe pumps – update concerning battery information (MDA/2018/035). Issued 14 November 2018. Manufactured by Caesarea Medical Electronics (CME) Ltd, a BD company – additional suitable battery identified for use in the T34 pump

- Batteries for the HeartStart MRx monitor/defibrillator may fail to charge or to provide power. Issued 29 November 2018. Philips M3538A lithium-ion batteries manufactured from 28 December 2017 to 20 March 2018 inclusive for the HeartStart MRx monitor/defibrillator may have an internal component failure.

Article citation: Drug Safety Update volume 12, issue 5: December 2018: 7.