Prescribing Points

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NHS
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Cinical Commissioning Group

This newsletter is written by the Medicines Optimisation Team, Oxfordshire CCG (OCCG), Jubilee House, Oxford Business Park South, Oxford, OX4 2LH. It is for all health professionals in Oxfordshire and is uploaded to the OCCG website. For queries, contact OCCG.medicines@nhs.net.

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Clarification of VTE treatment with dalteparin guidelines

In the previous Anticoagulation Special Edition Prescribing Points newsletter, it stated:

- Anticoagulation should be supplied by the GP if diagnostic investigations are expected to take longer than 1 hour from the time of first clinical suspicion of Pulmonary Embolism (PE).

Please note OUH is aware that dalteparin, apixaban and rivaroxaban are not usually stocked at practices. For suspected pulmonary embolism we would ask that GPs refer the patient to the medical referral line on 01865 227591, in line with our DOACs for Treatment VTE primary care guidelines. The medical team may ask the GP to prescribe the first dose of a DOAC prior to patients coming to hospital for investigation, or LMWH if the patient will attend the following day. In each case the risk will be assessed and the medical team have stated that there are times when they accept that it will not be practical to give the first dose in primary care if the medication will delay patients coming to hospital.

So What?

- The previous Anticoagulation Special Edition Prescribing Points newsletter has been corrected to reflect this.
- Please contact occg.medicines@nhs.net if you have any questions.

Avoiding the use of SGLT-2 inhibitors in patients with diabetes admitted to hospital

SGLT-2 inhibitors are increasingly being used to treat patients with Type 2 Diabetes. Examples of SGLT-2 inhibitors include Dapagliflozin/Forxiga®, Canagliflozin/Invokana®, Empagliflozin/Jardiance®, and Ertugliflozin/Sterglatro®.

There have been several case reports at OUH of diabetic ketoacidosis without significant hyperglycaemia (Euglycaemic Diabetic Ketoacidosis (euDKA)) in patients taking SGLT-2 inhibitors. Therefore, patients will have their SGLT-2 inhibitor stopped when admitted to hospital and it should be restarted by the GP **7 days following discharge**. This information will be detailed in the written section of the discharge letter.

Euglycaemic DKA **is a life threatening condition** and needs urgent treatment.

So What?

Action points for GPs

- **Remember sick day rules:** if patient is vomiting, has diarrhoea or is dehydrated, advise to STOP taking SGLT2 inhibitors until recovered. A Patient Information Leaflet on Sick Day Rules is available here.
- All patients on SGLT2 inhibitors who present with symptoms or signs suggestive of DKA should have their blood ketone concentrations checked as part of their initial assessment regardless of their blood glucose concentration. See GP Information here.
- **Elective surgical or procedural admission:** Be aware that patients need to stop SGLT-2 inhibitor treatment 72 hours before major surgery. Stopping will also be considered where possible before minor surgery, or before a procedure which requires the person to be nil by mouth.
- **Restart the SGLT-2 inhibitor when ALL of the following apply:**
  - 1 week after discharge OR when the patient had made a full recovery after discharge (whichever is later)
  - Once their eGFR is more than 45 ml/min
  - When the patient is aware of the risks, signs and symptoms of euglycaemic DKA
- **If the patient has had an episode of euglycaemic DKA:**
  - Do not restart SGLT-2 inhibitor
  - Update the allergy/intolerance information
  - Replace with a different medication for Type 2 diabetes which has proven cardiovascular benefits e.g. GLP-1 agonist. Look out for this change in the discharge letter.
- See local SGLT2 inhibitor resources available:
  - GP Information
  - Patient Information Leaflet
  - GP Checklist

PINCER Action Learning Set 3- Oxford/Bucks

In order to further support localities with PINCER, Oxford Academic Health Science Network (AHSN) will be rolling out additional PINCER Action Learning Set which will be catered towards new pharmacists based in practices or PCNs. All practices wishing to implement PINCER will be required to put forward a lead Pharmacist, GP or Nurse who will need to do an e-learning module (ALS1- elearning) and the associated face-to-face action learning session (Session 2 and Session 3). For further information please contact Ferdinand.manansala@oxfordahsn.org.

Please see more details below:

Action Learning Set	Date	Notes
Session 1: ALS1 (eLearning Module)	February 2020	• Access to the eLearning for Action Learning Set 1 (ALS1) is via the resource area (https://www.primis.nottingham.ac.uk/pincer/). • A PINCER account is needed to access this. PINCER account can be obtained via https://www.primis.nottingham.ac.uk/registration/registration/default.asp. • eLearning should be completed before attending an ALS2 workshop.
Session 2: ALS2 (Face-to-face)- Oxford/Bucks	31 March 2020; 10.00-12.30 Oxford Academic Health Science Network, Magdalen Centre North, Robert Robinson Avenue, OX4 4GA	Password: Pincer1 https://www.eventbrite.co.uk/e/pincer-action-learning-set-2-oxfordbucks-tickets-94165843573
Session 3: ALS3 (Face-to-face)	June 2020	Update after ALS2 have been completed.

Cannabis-based Medicinal Products

NICE published guidance on Cannabis-based medicinal products (NG144) in November 2019, in which NICE reviewed the use of these products in 4 clinical areas:

- **Intractable nausea and vomiting**
  NICE suggested to consider the use of nabilone as an add-on treatment for adults with chemotherapy-induced nausea and vomiting which persists with optimised conventional anti-emetics (when taking into account Adverse Drug Interactions).
- **Chronic Pain**
  NICE did not support the use of cannabis based products for treatment of chronic pain.
- **Spasticity**
  NICE reversed the recommendation they made in the draft guidance published earlier this year. The recommendation now is to offer a 4-week trial of THC:CBD spray to treat moderate to severe spasticity in adults with multiple sclerosis, if other pharmacological treatments for spasticity are not effective.
- **Severe treatment-resistant epilepsy**
  NICE produced Technology Appraisals recommending CBD for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. Use will be restricted to secondary care.

NICE guidelines are not subjected to statutory funding directions. They are advisory and their local implementation is therefore at the discretion of CCGs. Oxfordshire CCG will carefully consider NICE guidelines when developing strategies, planning services and prioritising resources as part of its on-going work to improve the quality of care and health outcomes for their population. However, OCCG reserve the right to depart from NICE guidance, if the CCG has good reason to do so, for example, the availability of resources and competing priorities. OCCG reserve the right to develop a local policy based on the principles within the clinical policies document and in accordance with local needs. Such a policy may or may not be consistent with

such NICE Guidance. NICE NG144 will be reviewed via the standard process within OCCG and against competing priorities. Please note:

- Sativex remains black listed and is not funded by OCCG.
- Nabilone remains black listed and is not funded by OCCG.

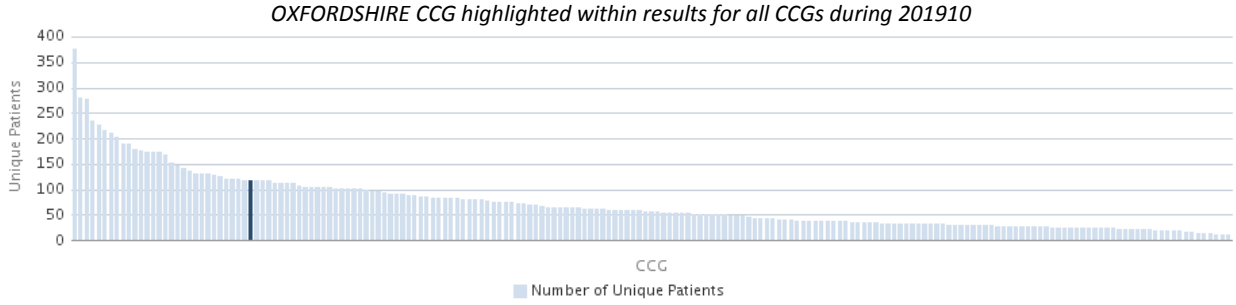
Co-prescribing of Oxycodone and Amitriptyline

Concomitant use of amitriptyline and oxycodone increases the risk of sedation, respiratory depression, coma and death because of additive Central Nervous System (CNS) depressant effects, as stated in the Summary of Product Characteristics here. Following the death of a patient who was prescribed both of these medications at the same time, a coroner's 'prevention of future deaths' report highlighted the need for both monitoring and caution when prescribing this combination of medications.

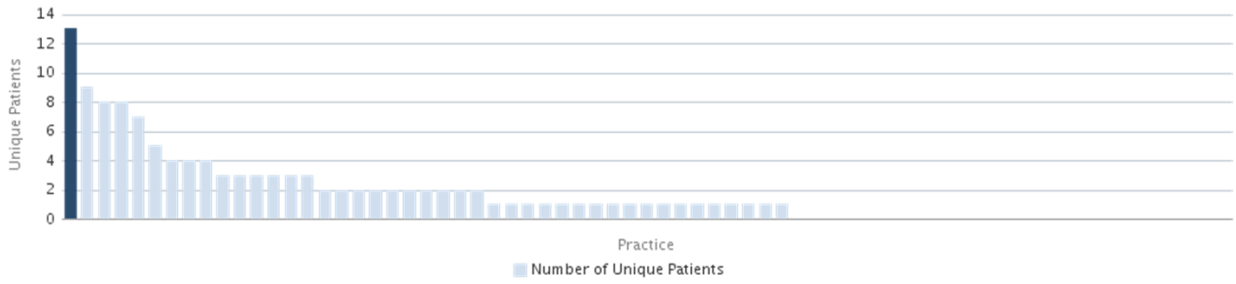
In Oxfordshire 118 patients have been identified as being co-prescribed with amitriptyline and oxycodone. Healthcare professionals are advised to identify these patients within their practice, and ensure arrangements for medications review and monitoring are in place.

Number of unique patients co-prescribed oxycodone and amitriptyline

OXFORDSHIRE CCG highlighted within results for all CCGs during 201910



Number of unique patients co-prescribed oxycodone and amitriptyline in Oxfordshire CCG, by practice



So What?

- Identify all patients who are co-prescribed oxycodone and amitriptyline and ensure their medications are reviewed.
- Medication review and monitoring for these patients should be carried out whenever there is a change in treatment regimen or increase in dosage, and at appropriate intervals.
- If concomitant use of this combination of medications is necessary, ensure patients are warned of the risks of over-sedation and advise them on when to seek medical attention.

Co-prescribing of Controlled Drugs

Controlled drugs (CDs) in Schedule 2 contain opioid drugs such as diamorphine as well as stimulants such as amphetamines. These drugs have a therapeutic value but are highly addictive and so their use is strictly controlled. CDs in Schedule 3 contain barbiturates and some benzodiazepines, and more recently included tramadol, gabapentin and pregabalin. There is less strict control of controlled drugs in Schedule 3 compared with those in Schedule 2.

Opioid-based painkillers prescribing in England and Wales has increased by more than 60% in the past decade - the number of such medicines dispensed in the community (excluding hospital settings) have risen from more than 14 million in 2008 to 23 million in 2018. Official statistics show tramadol was implicated in 220 drug-related deaths in England 2018 compared to just 7 in 1998.

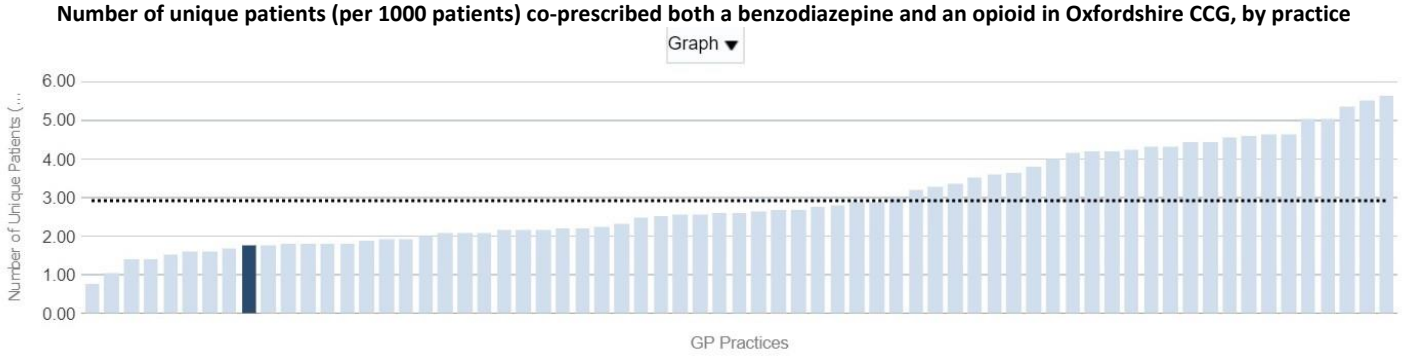
In 2019 Public Health England (PHE) published an evidence review on 'Dependence and withdrawal associated with some prescribed medicines'. The main findings of the review were:

- 1 in 4 adults have been prescribed these medicines, and half of them have been taking these medicines for at least 12 months
- the number of prescriptions for antidepressants is rising, particularly among women and older adults
- the highest prescribing rates are in areas with greatest social deprivation
- there is a recent fall in the number of prescriptions being given for opioid painkillers and tranquillisers, but dependence and withdrawal symptoms can be a problem with these drugs.

In order to support the work of controlled drug accountable officers and CCGs, NHSBSA have published some CD metrics on Epact2 and have chosen a number of specific areas of prescribing to focus on, based on the specialist opinion and available data. Figures pertinent to OCCG are shown in the table and graphs below.

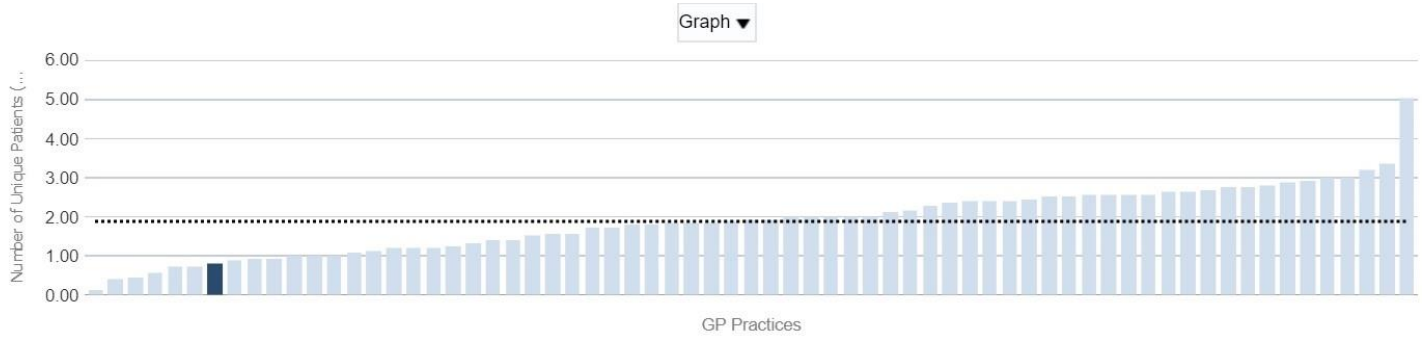
Metrics	Total number of unique patients identified across OCCG between Aug and Oct 2019 (3 months)
Co-prescribing of both **gabapentin and an opioid** in the same month	2,056
Co-prescribing of both a **benzodiazepine and an opioid** in the same month	2,048
Co-prescribing of both **pregabalin and an opioid** in the same month	1,414
Co-prescribing of both **gabapentin and a schedule 2 controlled drug** in the same month	591
Co-prescribing of both **pregabalin and a schedule 2 controlled drug** in the same month	508

Number of unique patients (per 1000 patients) co-prescribed both a benzodiazepine and an opioid in Oxfordshire CCG, by practice

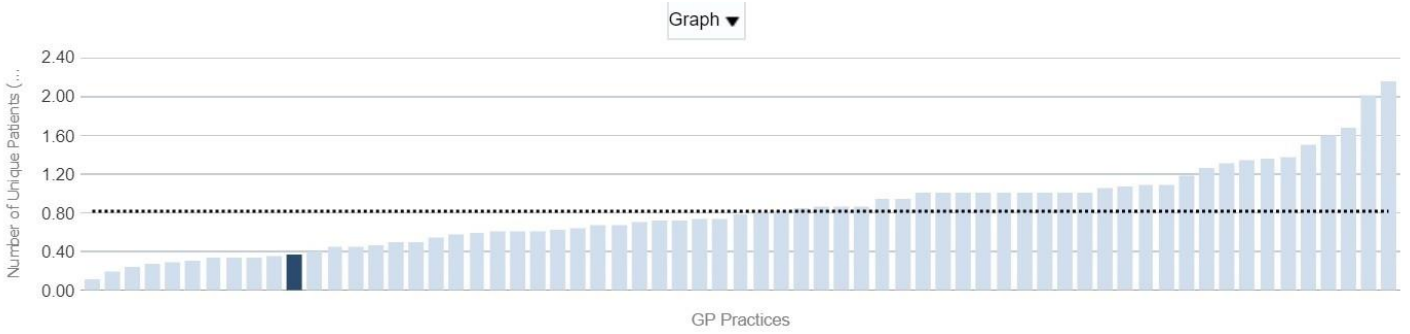


Number of unique patients (per 1000 patients) co-prescribed both gabapentin and an opioid in Oxfordshire CCG, by practice

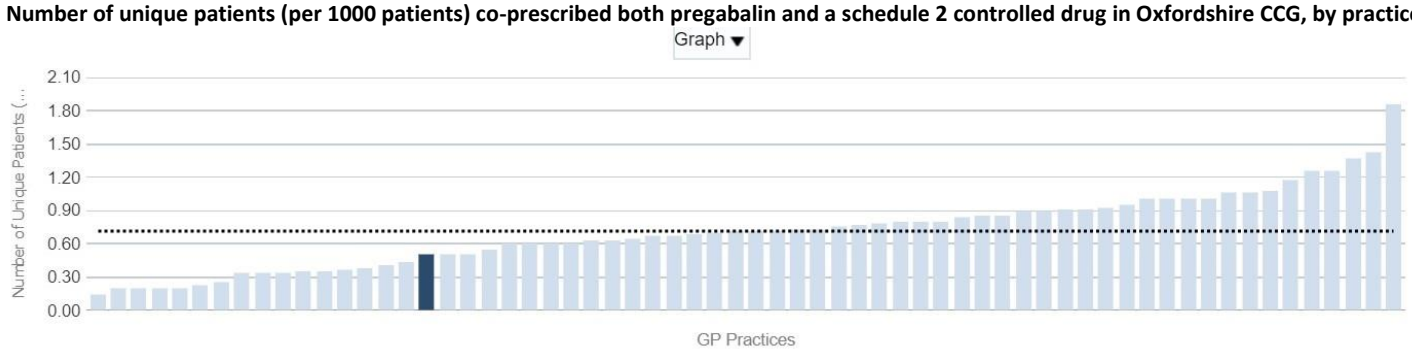
Number of unique patients (per 1000 patients) co-prescribed both pregabalin and an opioid in Oxfordshire CCG, by practice



Number of unique patients (per 1000 patients) co-prescribed both gabapentin and a schedule 2 controlled drug in Oxfordshire CCG, by practice



Number of unique patients (per 1000 patients) co-prescribed both pregabalin and a schedule 2 controlled drug in Oxfordshire CCG, by practice



Other relevant resources:

- NICE Clinical Knowledge Summary: Opioid dependence
- Care Quality Commissioning (CQC) annual update report (2018)
- NICE Guideline NG46: Controlled drugs: safe use and management
- OCCG Guideline: Opioid Prescribing Guidelines for Non Cancer Pain
- OCCG Guideline: Guideline for the Management of Neuropathic Pain in Primary Care
- Local Guidance for opioid reduction in primary care

So What?

- Identify patients in your practice who are on any of this combination of medications.
- Review patient's medications and consider if this combination or the dosage is appropriate or necessary.
- If concomitant use of this combination of medications is necessary, ensure patients are warned of the associated risks and advise them on when to seek medical attention.
- Please contact the Medicines Optimisation team at occg.medicines@nhs.net if you would like practice level data; or if you want us to build a search remotely for you.

Potential Under-recognised Risk of Harm from the use of Propranolol

There has been a steady rise in the number of propranolol prescriptions issued to NHS patients. Between 2012 and 2017 there was a 33% increase in the number of deaths reported as being linked to propranolol overdose. In 2017, 52 deaths were recorded as linked to propranolol overdose. The HSIB (Healthcare Safety Investigation Branch) have published a report on the potential under-recognised risk of harm from propranolol overdose. Seven safety recommendations have been made as a result of this investigation. For more information please see the report here.

So What?

- One of the recommendations is for PrescQIPP to support subscribers to identify the potential risk of prescribing propranolol to patients in at risk groups. A set of search tools to support identification of patients will be made available on PrescQIPP soon.

APCO Updates

Oral Vitamin B Supplementation in Alcoholism

The Regional Medicines Optimisation Committee (RMOC) reviewed the use of vitamin B supplementation in alcoholism, taking into account relevant guidance published by NICE and NHS England as well as information from other specialist sources. The local formulary has been updated as advice is summarised as follows:

Vitamin B complex preparations

• Due to a lack of evidence on their efficacy and safety, vitamin B complex preparations (vitamin B compound and vitamin B compound strong tablets) **should not** be prescribed for prevention of Wernicke's Encephalopathy (WE) in alcoholism.

• Vitamin B complex preparations **should not** be prescribed for preventing deficiency or for maintenance treatment following treatment for deficiency.

• Vitamin B complex preparations **should not** be prescribed as dietary supplements. Patients who wish to use them for dietary supplementation should be advised to purchase them over the counter.

• **Vitamin B compound strong tablets may be prescribed** on a short-term basis (10 days) for patients at risk of refeeding syndrome. This also applies to patients who are not harmful or dependent drinkers.

• In rare cases where there might be a justifiable reason for prescribing vitamin B complex e.g. medically diagnosed deficiency or chronic malabsorption, **vitamin B compound strong** and not vitamin B compound should be prescribed as it represents better value for money.

Thiamine

In line with NICE guidance, oral thiamine should be prescribed for the prevention of WE to harmful or dependent drinkers in whom any of the following apply:

- They are malnourished or at risk of malnourishment
- They have decompensated liver disease
- They are in acute withdrawal
- Before and during a planned medically assisted alcohol withdrawal

The recommended dose is 200 to 300 mg daily in divided doses. Thiamine should be continued for as long as malnutrition is present and/or during periods of continued alcohol consumption. Following successful alcohol withdrawal, thiamine should be continued for 6 weeks. If after this time the patient remains abstinent and has regained adequate nutritional status, thiamine should be discontinued. Thiamine should be restarted if the patient starts drinking again. Continual need for thiamine should be reviewed at appropriate intervals which may depend on individual patient's circumstances.

So What?

- Review all existing patients prescribed vitamin B complex preparations with a view to stopping treatment in all but exceptional circumstances (e.g. medically diagnosed deficiency due to lifelong or chronic condition, or following surgery that results in malabsorption).
- If it is considered appropriate to stop, treatment may be stopped immediately.
- The decision to discontinue treatment should be carefully explained to the patient, and should emphasise the positive aspects of discontinuing the prescribing of drugs with a low clinical value.
- Advise patients who wish to use these vitamin B preparations as dietary supplements to purchase them over the counter.

Lacosamide, Zonisamide & Perampanel

Lacosamide, Zonisamide and Perampanel were first introduced to OCCG with Shared Care Protocols (SCP) accompanying their use. As per the Summary of Product Characteristics, there are no special monitoring requirements for these medications. On the Oxfordshire formulary, most antiepileptic drugs are now listed as Amber Continuation. To bring Lacosamide, Zonisamide and Perampanel in line with other antiepileptic drugs on the OCCG formulary and reduce need for unnecessary SCPs, their formulary status has been updated to Amber Continuation. The GP responsibilities are as follows:

- Prescribe drug according to directions provided by specialist.
- Advise the Hospital Consultant of any clinical changes or adverse effects where appropriate.
- Monitor for adverse effects.
- Monitor seizure control and seek specialist advice or referral as appropriate

So What?

- Please note the SCPs for Lacosamide, Zonisamide and Perampanel have been removed from ClinOx.
- GPs should continue to prescribe the medication on advice from the specialist.

Supply Issues and Product Discontinuation

Picato® (ingenol mebutate): Market Authorisation Suspension

Picato® (ingenol mebutate) is used for the treatment of actinic keratosis in adults when the outer layer of the skin affected is not thickened or raised. Final results from a study comparing Picato® (ingenol mebutate) to another medicine for actinic keratosis (Imiquimod) indicate a higher occurrence of skin cancer in the treatment area with Picato®. Following the growing concerns on the possible risk of skin malignancy, in January 2020, the marketing authorisation for ingenol was suspended as a precautionary measure while European Medicines Agency (EMA) continues to investigate. This is an EU-wide suspension and batches of ingenol mebutate are being recalled to pharmacy level with immediate effect.

The local formulary has been updated to reflect this change.

So What?

- Stop prescribing ingenol and consider other treatment options, as appropriate.
- Advise patients to be vigilant for any skin lesions developing within the treatment area, and to seek medical advice promptly should any occur.

Supply Issue: Phenytoin 100mg capsules

Accord is out of stock of phenytoin sodium 100mg capsules until early May 2020.

Phenytoin is classified by the Medicines and Healthcare products Regulatory Agency (MHRA) as a Category 1 anti-epileptic drug; which means it is advisable for patients to be maintained on a specific manufacturer's product. An alternative phenytoin sodium 100mg capsules manufactured by Flynn Pharma is available, however switching to an alternative formulation requires monitoring and may also require specialist support, advice or referral.

So What?

- Identify all patients currently prescribed phenytoin sodium 100mg capsules and determine the brand of phenytoin 100mg capsules the patient takes;
- If the patient takes a phenytoin 100mg capsule which is not manufactured by Accord, ensure patients are maintained on the same product;
- If the patient takes a phenytoin sodium 100mg capsule which is manufactured by Accord, the following advice should be followed:
  - switch patients to phenytoin sodium 100mg capsules manufactured by Flynn Pharma, where clinically appropriate and monitor patients accordingly.
  - if phenytoin sodium 100mg capsules manufactured by Flynn Pharma are not clinically appropriate then alternative phenytoin formulations should be considered.
  - for all switches, ensure monitoring requirements are undertaken accordingly.
- Ensure that patients are maintained on the same manufacturer's brand of phenytoin preparation going forward and that the brand is clearly stated on the prescription.
- For more information please see the Supply Disruption Alert here.

Supply Issue: Freestyle Libre

There is currently a temporary supply disruption with Freestlye Libre in the community. Abbott, the manufacturer of Freestyle Libre, has issued a statement advising of the temporary delays in fulfilling orders of FreeStyle Libre sensors. Order delays have been reduced substantially since January and order should now be received approximately one week after placing it. Community pharmacy teams unable to obtain supplies of the sensors are advised to refer any affected patients back to their prescriber for consideration of alternative monitoring methods in the interim period (see guideline for Blood Glucose Monitoring).

So What?

- Advise patients to only order what they need and then re-order as required. Patients should be prescribed no more than 2 sensors per month as per Patient Agreement Form.
- Consider alternative monitoring methods in the interim period

Supply issue – Salbutamol 2mg/5ml Syrup

There is currently a temporary supply issue with Salbutamol 2mg/5ml syrup until the end of February 2020.

So What?

If supplies are needed then alternatives are available:

- Patients should be reviewed to ensure that oral is the most appropriate route of administration. Inhaled therapy is the preferred method of administration and should be used whenever possible as it is more effective and has fewer side-effects
- Unlicensed import of salbutamol 2mg/5ml syrup (Clinigen and Alium Medical have confirmed they have availability, there may be other importers)
- Salbutamol 2mg or 4mg tablets - these tablets can be crushed and dispersed in water, however this is unlicensed.

E-cigarette Use or Vaping

The MHRA issued a safety alert on e-cigarette or vaping and urged healthcare professionals to have high level of suspicions in patients presenting with respiratory symptoms, particularly when there is a history of e-cigarette use or vaping in the past 30 days. This alert was in response to the investigations in the USA on the recent outbreak of e-cigarette or vaping associated lung injury, also known as EVALI, and the subsequent two potential EVALI cases reported in the UK, both of which had a fatal outcome.

Since there are no standard diagnostic criteria, the MHRA has devised UK case definitions of EVALI to facilitate identification, on the basis of expert advice:

Probable cases
Cases should be considered probable if they meet ALL of the following criteria:
1) Using an e-cigarette or vaping in 30 days prior to symptom onset
AND
2) Pulmonary infiltrate, such as opacities on plain-film chest X-ray, or ground glass opacities on CT chest
AND
3) Absence of respiratory infection. Minimum criteria to be excluded:

- Negative respiratory viral screen (e.g. influenza, adenovirus, rhinovirus, coronavirus)
- Negative testing for all other clinically-indicated respiratory infectious diseases (e.g. urine antigen for Streptococcus pneumoniae and Legionella, sputum culture, bronchoalveolar lavage culture, blood culture and opportunistic respiratory infections if appropriate)

AND
4) No evidence of alternative diagnosis (e.g. cardiac, autoimmune, malignancy)

Possible cases
Cases should be considered possible if they meet criteria 1, 2, and 4, but a respiratory infection is identified via culture or PCR, and the clinical team believes infection is not the only cause of underlying lung injury OR the minimum criteria to exclude infection are not met due to testing not having been performed and the clinical team believes the infection is not the only cause of the underlying lung injury.

Cases that do not strictly meet the criteria
Cases that do not strictly meet the criteria, for example if use of e-cigarette or vaping stopped more than 30 days before symptom onset, are still of interest and should be reported.

So What?

- Healthcare professionals should be vigilant if patients present with respiratory symptoms and there is a history of e-cigarette use or vaping in the past 30 days.
- For all patients, ask about e-cigarette use or vaping routinely as you would do about cigarette smoking.
- Report any suspected adverse reactions or safety concerns associated with use of e-cigarettes or vaping via the Yellow Card Scheme. If you report a case of EVALI, please specify if it meets the criteria for a probable or possible case and provide full details of the vaping product, vaping history, and other potentially relevant clinical details. See the safety alert for full details.

Ondansetron in the First Trimester of Pregnancy

Outside of their authorised indications, a number of drugs are commonly used to treat nausea and vomiting in pregnancy (NVP), such as cyclizine, promethazine, prochlorperazine, metoclopramide and ondansetron. Recent epidemiological studies indicate that use of ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate. The MHRA advised that if a clinical decision is to offer ondansetron in pregnancy, women must be counselled on the potential benefits and risks of use, both to her and to her unborn baby and the final decision should be made jointly.

More information on the management of NVP can be found on the following resources:

- NICE Clinical Knowledge Summaries: Nausea/ vomiting in pregnancy
- Specialist Pharmacy Service (SPS): How can nausea and vomiting be treated during pregnancy?

So What?

- Report any suspected adverse drug reactions in the mother or child, including adverse pregnancy outcomes, following use of a medicine in pregnancy via the Yellow Card Scheme.

Nexplanon (Etonogestrel) Contraceptive Implants: New Insertion Site

Following concerns regarding reports of neurovascular injury and implants migrating to the vasculature (including the pulmonary artery), possibly due to deep insertion, insertion in an inappropriate site, and insertion in thin arms; the MHRA has issued amended advice on the insertion site for Nexplanon contraceptive implants.

The amended advice is that subdermal insertion of the implant is the best way to avoid injury, and use of the new site should minimise the risk of migration to the lung and neurovascular injury in case of inadvertent deep insertion. The insertion site is located in an area overlying the triceps muscle which is generally free of major blood vessels and nerves. The updated instructions have been added to the product information for Nexplanon and a letter has been sent to healthcare professionals. The Faculty of Sexual and Reproductive Healthcare (FSRH) has also issued a statement.

So What?

- An implant should be inserted subdermally by a healthcare professional who has been appropriately trained and accredited.
- Review the updated guidance for how to correctly insert the implant.
- Localise any implant that cannot be palpated (for example, by imaging the arm) and remove it at the earliest opportunity.
- Implants inserted at the previous site that can be palpated should not pose a risk and do not need to be moved to the new site; only replace implants if you have concerns regarding their location or if routine replacement is due.
- Report any suspected side effects to Nexplanon on a Yellow Card, including difficulties with insertion or adverse incidents from migration of the implant or related to its removal.