NHS
North Central London
Clinical Commissioning Group

Discontinuation of Phyllocontin® (aminophylline) 225mg and 350mg modified release tablets

To:	GPs and primary care pharmacists
From:	NCL CCG Medicines Management Teams
Date:	17th March 2021

Background

Aminophylline 250mg and 350mg modified release tablets (Phyllocontin®) are methylxanthine medications used in the UK for the treatment and prophylaxis of bronchospasm associated with asthma, COPD and chronic bronchitis. On February 12th DHSC announced that Phyllocontin® will be discontinued in the UK based on a commercial decision; stock of the 225mg tablets is expected to be exhausted by 30th March 2021 and the 350mg tablets is expected to be exhausted by 5th April 2021.

The DHSC have published a Supply Disruption Alert to provide advice and information on safe switching from Phyllocontin® to an alternative theophylline oral preparation, where appropriate. This memo summarises the DHSC guidance and integrates advice from Specialists in NCL.

Guidance for NCL GPs and primary care pharmacists

Summary for adult patients:

1) GPs and practice-based pharmacists to identify all patients prescribed Phyllocontin® (aminophylline) Continus 225mg and Forte Continus 350mg modified-release tablets
2) Make early contact to consider for a respiratory review or a switch strategy.
    a. Where the patient is currently under the care of a respiratory specialist for the medication, consider liaising with the specialist for further advice, where clinically appropriate.
    b. Practices may wish to liaise with their community pharmacies on local stock levels.
    c. Review whether a methylxanthine is still required (as it may be of minimal benefit or have a significant side effect profile).
    d. Ensure an up-to-date asthma self-management plan is in place if applicable; advise the patient or patient's carer not to interrupt inhaled corticosteroid medications and ask if a repeat prescription of steroid inhaler is required. Discuss adherence and optimise inhaler technique (if able to do so in this consultation).
    e. If treatment with a methylxanthine is deemed necessary to continue and patient is adherent to therapy, consider switching patients to theophylline tablets (prescribed by brand - Uniphyllin Continus®). Consider dose adjustment if required - see below for an appropriate conversion and necessary monitoring (see advice below) to be carried out by prescribers.
3) A switch should only be undertaken in patients who are tolerating treatment and their baseline theophylline plasma levels are within therapeutic range. Plasma theophylline levels taken within the past six months are an acceptable indicator (but check whether the baseline level on record is a peak- or trough-plasma level before interpretation).
4) If a patient has switched treatment, consider a trial observation period over three months to determine if true benefit is seen. Agree a plan with the patient for follow up to stop or continue/dose escalate therapy accordingly.
5) Seek support from specialists for patients with unstable asthma or if deemed essential

Summary for paediatric patients:

1) Make early contact with the patient or carer to allow time for treatment review or switch strategy
2) Refer to the originating secondary/tertiary care centre to decide on further management.

Switching medications

The following advice should be used to support switching to Uniphyllin Continus® (oral theophylline tablets) in patients for whom treatment with a methylxanthine is still required

1) As noted above, a switch should only be undertaken in patients who have been tolerating treatment with aminophylline, experiencing benefit and who have baseline theophylline plasma levels (within the past six months) within therapeutic range.
    a. If there are any concerns (e.g., the patient is not realising benefit from therapy), consider referring back to the initiating specialist/centre to review the overall management of the condition and/or adjustment in therapy.
2) If a baseline level is not available, the patient should have a baseline blood test to ensure they are within therapeutic range.
    a. If within range, switch the patient to oral theophylline (see below).
    b. If the patient is not within therapeutic range at baseline consider the following prior to switching therapy:
        i. Address factors contributing to problems in adherence
        ii. Review potential drug interactions - concurrent medications that may affect theophylline level (e.g., macrolides, ciprofloxacin etc)
        iii. Review for other factors that affect theophylline clearance (e.g., heart/liver failure, COPD, viral infections, smoking status etc; if patient is a smoker, offer 'very brief advice', and advise that smoking cessation should only be undertaken with a healthcare professional as smoking cessation may affect the theophylline level).
3) In patients who have all factors reviewed and it is still appropriate to continue therapy with a methylxanthine, switch therapy to oral theophylline (see below). Await results from the post-switch serum theophylline before considering a dose adjustment.
4) The following conversions to theophylline prolonged release tablets (Uniphyllin Continus®) are suggested by the DHSC (see Table 1 below for a comparison between products):
    - Patients taking 225mg aminophylline should be converted to theophylline 200mg
    - Patients taking 350mg aminophylline should be converted to theophylline 300mg
    - Patients taking 450mg aminophylline should be converted to theophylline 400mg
5) Patients should take all their remaining aminophylline before switching to theophylline
6) Patients should be instructed to take their first theophylline dose when their next aminophylline dose would have been due.
7) Counsel patients that there is no change in how they take their new medication e.g. swallow whole, do not crush, break or chew. Continue to take at the same time of day at regular intervals. If they forget to take a dose but remember within 4 hours, the tablet can be taken straight away. The next dose should then be taken at the normal time. Beyond 4 hours, please contact your doctor or pharmacist for advice (alternative treatment may need to considered).

Monitoring

Therapeutic drug level monitoring of theophylline should be undertaken when patients are switched from aminophylline to theophylline, and when clinically indicated (with oversight from specialists if needed, i.e. suspected adverse effect/worsening disease control.

1) Plasma theophylline concentration should be measured 5 days following a switch.
2) The blood sample should be arranged to be taken 4-6 hours post-dose. A list of available phlebotomy clinics in NCL can be found here: Link to phlebotomy clinics in NCL
    a. The locally agreed phlebotomy turnaround time for plasma theophylline results is 24 hours.
    b. Where toxicity is suspected or patient exhibits symptoms of toxicity, consider discussion with specialist/medical team and withholding next doses until results have been received and reviewed.

3) Waiting times for phlebotomy appointments vary (from same day to 4 weeks) depending on phlebotomy clinic site (see footnote for current waiting time[1]). A phlebotomy appointment should be booked before switching, to co-ordinate an appointment 5 days following switch.
4) The plasma theophylline concentration:
   a. Should be 10-20mg/L (55-110 micromole/L) in most individuals.
   b. A lower plasma theophylline concentration of 5-15mg/L may be effective.
5) If the plasma theophylline concentration is within an effective range without adverse effects, continue with the same dose. The dose may be titrated up or down based on plasma theophylline level, efficacy and potential development of adverse effects.
   a. If the clinician has any reservation in dose titration, consider contacting the specialist team.
6) Adverse events can occur within the 10-20mg/L range. The frequency and severity of adverse effects increases at concentrations above 20mg/L.
   a. Side effects that could indicate toxicity include nausea, vomiting, epigastric pain, haematemesis, restlessness, hypertonia, exaggerated limb reflexes, convulsions, hypotension and sinus tachycardia.
   b. Consider liaising with the specialist/medical team for advice and guidance.
7) Where the monitoring results are released outside general practice working hours and the plasma levels are at or above critical limits (>25mg/L) or toxicity is suspected, the phlebotomy team will contact and report this to the out of hours GP for appropriate action to be taken.
8) Consider a trial observation period over three months to determine whether the patient is benefitting from therapy and no adverse effects are experienced.

Table 1 – Comparison of aminophylline and theophylline oral modified release preparations

Product	Adult dose	Paediatric dose	Administration
Aminophylline (Phyllocontin Continus®) Prolonged release tablets (225 and 350mg)	225 mg twice daily (may be titrated to higher dosage as required)	10 mg/kg twice daily. Some children with chronic asthma require and tolerate much higher doses (11-18 mg/kg twice daily).	Tablets should be swallowed and not chewed.
Theophylline (Uniphyllin Continus®) Prolonged release tablets (200, 300 and 400mg)	200 mg twice daily, titrated to either 300 mg or 400 mg dependent on therapeutic response.	9 mg/kg twice daily. Some children with chronic asthma require and tolerate much higher doses (10-16 mg/kg twice daily).	These tablets must be swallowed whole and not broken, crushed or chewed as doing so may lead to a rapid release of theophylline with the potential for toxicity.
Oral aminophylline tablets (extended release) have 90-100% bioavailability. Salt factor for aminophylline ~ 0.8 ***225mg aminophylline ~180mg theophylline***			

If you have any queries please email your borough MMT.

Barnet MMT email:	**Camden MMT email:**	**Enfield MMT email:**
nclccg.barnetmmt@nhs.net	mmt.camdenccg@nhs.net	enfccg.medicinesmanagement@nhs.net
Haringey MMT email:		**Islington MMT email:**
harccg.medicines@nhs.net		mmt.islington@nhs.net

[1] Current waiting time: Royal Free: Edgware Community Hospital 4 weeks, Royal Free Hampstead 2 weeks, Chase Farm sites both 2 weeks. North Middlesex University Hospital: Evergreen same day, The Laurel 3 days, Forest PCC 8 days. Whittington Health: All sites 5 days. UCLH: Maximum 3 days at all sites, some same day availability. CLCH: Same day