COMMISSION ON HUMAN MEDICINES

Title of paper: Assessment of benefits and risks of non-prescription codeine oral solution and risk of recreational use **Type of paper:** For advice	
Products: Codeine Linctus BP Bells healthcare codeine linctus 15mg/5ml oral solution Care codeine 15mg/5ml oral solution Pulmo Bailly Thornton & Ross codeine phosphate 25mg/5ml oral solution Co-codamol 30mg/500mg/5ml oral solution	**Assessor:** [redacted]
Active constituents: Codeine	**Previous Assessments:** N/A
MAHs: LCM Limited Bell Sons & Company (Druggists) Limited Thornton & Ross Limited Pinewood Laboratories Limited Dendron Brands Limited Wockhardt UK Limited	**Legal status:** POM and P
Therapeutic classification: Analgesics	

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Executive Summary

This paper discusses the legal status for all strengths of codeine oral solutions (7mg/5ml, 15mg/5ml and 25mg/5ml). The current indication is for 'the relief of an unproductive dry or painful cough' in adults and adolescents aged 12 years to 18 years without compromised respiratory function.

Codeine has been used as an antitussive for many years, although the evidence for efficacy is sparse. Randomised controlled trials have shown little efficacy in subacute cough whereas there is evidence of efficacy for morphine in the treatment of chronic cough. Codeine is a prodrug, which is metabolised into morphine via the cytochrome p450 2D6 enzyme, however this enzyme is polymorphic and patients' ability to metabolise codeine is dependent on its status and whether the patient is a poor, intermediate, extensive or rapid metaboliser.

Safety concerns have been raised concerning the combination of codeine linctus, promethazine and fizzy drinks to make the recreational drink known as 'Purple Drank' or 'Lean'. Both codeine and promethazine are pharmacy medicines, however the combination is not authorised and therefore is not considered a medicine. Fatalities have been reported of popular music artists, who have become addicted to the drink. However, there is limited evidence of such fatalities specifically related to Purple Drank being reported in the UK.

The Commission is asked to consider whether low strengths of codeine oral solution may safely be supplied without a prescription or upregulated to being available on prescription only in line with the higher strength codeine solutions.

1. INTRODUCTION

This paper discusses the considerations around access to codeine oral solutions as Pharmacy-only medicines and seeks the advice from the Commission on whether the criteria for supply only on prescription are considered to be met for these products.

2. BACKGROUND AND LICENSING HISTORY

Codeine is an opioid medicine which is metabolised into morphine which will produce analgesia. Codeine oral solutions are available as non-prescription medicines for supply under the supervision of a pharmacist ('P') for the treatment of dry cough. However codeine linctus as a 'P' medicine is not efficacious in the treatment of pain therefore is only indicated as an antitussive.

At present there are 6 marketing authorisations (MAs) for codeine oral solution, of which 4 are P products (7mg/5ml and 15mg/5ml) and 2 as prescription only medicines (25mg/5ml and one oral solution containing codeine 30mg and paracetamol 500mg/5ml) (annex I). The non-prescription codeine oral solutions (herein referred to codeine linctus) are available and marketed in pack sizes of 200ml and 2L.

In 2005, the Committee on Safety of Medicines (CSM) examined the availability of non-prescription codeine-containing analgesics following reports of dependence and medication overuse headache and considered options for regulatory action. CSM made a number of recommendations although CSM considered that supply under the supervision of a pharmacist continued to be appropriate, as the incidence of dependence and abuse (even taking into account underreporting) was considered very low and no further restrictions were placed on codeine linctus oral solutions.

In 2009, the Commission of Human Medicines (CHM) revisited this issue as reports of dependence/addiction had not decreased since 2005, therefore CHM considered that further risk minimisation measures were need, as those implemented in 2005 appeared to be insufficient on their own. The CHM noted that there was no evidence to suggest that usage of non-prescription codeine, or addiction to, or misuse of 'P' medicines containing codeine, was increasing but agreed a number of further labelling updates on the risk of dependence and responsible promotion of these products.

In 2019, during the review of dependence/addiction to opioids in the treatment of acute non-cancer pain, codeine availability without prescription was further explored and the number of reports of abuse were identified as increasing. Therefore, CHM gave provisional advice that the classification of codeine met one of the Prescription Only criteria of the Human Medicines Regulations 2012. Progression on this advice was delayed owing to the onset of the pandemic, however, a number of additional warnings were recommended for inclusion on the label for all opioids and in the product information for all prescribed opioids including codeine. As codeine linctus is not a prescribed medicine, and not indicated for the treatment of pain, the product information in the Summary of Product Characteristics (SmPC) and patient information leaflets (PIL) were unchanged.

Since 2019, there have been increasing reports in the media of the misuse of codeine linctus and promethazine as primary ingredients of the recreational drink named 'Purple Drank' which has led to addiction to codeine and the deaths of popular music artists in the US. The MHRA have also received increasing numbers of reports of diversion and reports of criminal activity in the acquisition of codeine linctus in the UK. This paper seeks the advice of the Commission on the continued availability of codeine linctus without prescription.

3. EFFICACY

3.1. Metabolism of codeine

Codeine is considered to be a 'weak' opioid as its potency is approximately 1/10th of morphine. However, codeine is a prodrug that is metabolised into morphine and morpine-6-glucuronide, both potent opioid agonists, which are thought to produce the main effect of codeine either as an analgesic or antitussive. Codeine is metabolised into morphine via CYP2D6, a polymorphic isoenzyme whose phenotype is governed by genetics. In general, patients can be poor metabolisers, intermediate, extensive or ultra-rapid metabolisers. The activity of the enzyme is also influenced by interaction with some concomitant medicines; therefore a rapid metaboliser is at risk of opioid toxicity even at therapeutic doses. Morphine is subsequently metabolised by glucuronidation into morphine-6-glucoronide via UDP-glucuronosyltransferase (UGT) 2B7. All other metabolites are inactive[1].

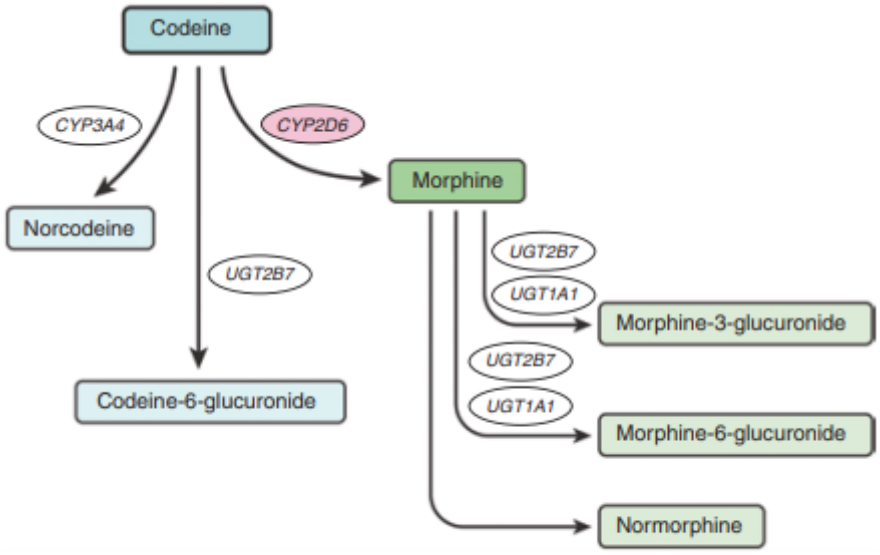

Figure 1 Codeine metabolism pathway.

[1] Crews KR, Gaedigk A, Dunnenberger HM, Klein TE, Shen DD, Callaghan JT, Kharasch ED, Skaar TC; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012 Feb;91(2):321-6. doi: 10.1038/clpt.2011.287. Epub 2011 Dec 28. PMID: 22205192; PMCID: PMC3289963.

3.2. Efficacy of codeine in cough

Codeine linctus is authorised as an antitussive for non-productive cough. There is a lack of consistent evidence for efficacy of low-dose codeine as an antitussive.

Cochraine review of Over The Counter (OTC) medicines for cough 2014[2]
Two randomised studies were identified, testing codeine in the home and in the laboratory. One showed that 30mg four times daily was no more effective than placebo. The other study only tested 50mg as a single dose and showed a reduced subjective score, 90 minutes after treatment although not significantly different from placebo. One additional study in children also showed no significant difference between codeine and placebo.

Morice and Kardos 2016[3]
This review highlights the paucity of evidence supporting the clinical use of codeine for antitussive activity. The authors point out that codeine is metabolised into morphine, which has been demonstrated in randomised controlled trials to have efficacy, although only in about third to half of patients with chronic cough. Codeine has been reported in some studies to have no effect on a cough challenge or the urge to cough whereas others have shown a small but significant effect. Overall, the authors conclude there is no convincing evidence of efficacy.

Speich et 2018[4]
This review examines treatments in primary care for subacute cough. Acute cough lasts <3 weeks, subacute cough lasts 3 – 8 weeks and chronic >8 weeks. Subacute cough is defined by the American College of Chest Physicians (ACCP) as cough that *"…lasts no longer than 8 weeks; the chest radiography findings are negative ruling out pneumonia; and the cough eventually resolves, usually on its own"*. However, some treatments have been proposed for alleviation, including cough mixtures containing codeine. The authors conducted a systematic review and meta-analysis of randomised clinical trials in patients ≥16 years of age with subacute cough. The authors also included some studies with slightly longer or shorter duration of cough, or non-specified duration of cough, to evaluate further potentially pertinent evidence. Studies including patients with a medical history of chronic respiratory disease were excluded. The risk of bias was assessed following Cochrane standards. The authors compared results for cough scores, using the standardised mean differences (SMD) as the only clinically comparable outcome. However, the overall review had limitations as very few studies were identified overall, and cough scores and timepoints of measurements differed. Similarly, some studies included patients with shorter or longer durations of cough. Only one study (Woodcock et al 2010) was described that compared codeine with placebo or a nociception opioid 1 (NOP1) agonist. Overall, the authors highlighted the limited available evidence on therapeutic

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[2] Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub5.

[3] Morice A, Kardos P. Comprehensive evidence based review on European antitussives. BMJ Open Resp Res 2016;3:e000137.
doi:10.1136/bmjresp-2016- 000137

[4] Speich B, Thomer A, Aghlmandi S, Ewald H, Zeller A, Hemkens LG. Treatments for subacute cough in primary care: systematic review and meta-analyses of randomised clinical trials. Br J Gen Pract. 2018 Oct;68(675):e694-e702. doi: 10.3399/bjgp18X698885. Epub 2018 Sep 10. PMID: 30201828; PMCID: PMC6145999.

options for subacute cough, although shows that symptoms diminish over time in a self-limiting disease.

Woodcock et al 2010[5]

This randomised controlled trial (RCT) compared placebo with codeine and a NOP1 agonist (SCH486757) in patients with a history of persistent cough following symptoms indicative of a viral upper respiratory tract infection, with onset between 14 to 90 days prior to the prescribing visit. NOP1 is a g-protein coupled receptor with significant homology to the μ, κ and δ opioid receptors. SCH486757 is a potent and highly selective NOP receptor agonist and was also shown in guineapigs to have comparable oral antitussive activity to codeine in a capsaicin-evoked cough model.

The RCT was a multicentre, double-blind, parallel-group study. The primary endpoint was change in cough severity scores for SCH486757 compared to placebo. The key secondary outcome of change in objective daytime cough counts. Patients received 1) SCH486757 100mg twice daily, 2) codeine 30mg twice daily, 3) placebo twice daily. Patients with a history of lung disease or other systemic disease or current or ex-smokers of more than 10-pack-years were excluded. Patients taking ACE inhibitors or opiates were also excluded. Pregnant or breast-feeding patients were excluded and those with child-bearing potential were required to use birth control. Patients recorded subjective cough scores on a 0 – 3 point scale with 0 representing no cough and 3 severe, hard to tolerate, interfering in sleep and daily living. Ninety-one patients were enrolled, 27 randomised to SCH486757, 34 to codeine and 30 to placebo. There were no difference in gender, ethnicity, height or weight. Two subjects dropped out because of adverse events (one from each active). There were no significant differences in the primary end point of change of average cough severity scores between either active and placebo. Cough severity scores declined gradually in all three groups over the 5 days of treatment. Objective cough measurement using a 'Lifeshirt' at baseline, day 1 and day 5 were undertaken in 74 subjects (with technical difficulties in the remaining 17 patients). On day 1, codeine reduced cough counts by a median of 0.1 coughs/h and placebo 2.8 coughs/h. On day 5, codeine reduced cough count by a median of 13.8 coughs/h and placebo 7.8 coughs/h. Median changes in cough count from baseline were not statistically significant over the full 8 hours of cough monitoring (SCH486757 reduced cough counts by a median of 8.1 coughs/h, codeine by 14.4 coughs/h, and placebo by 2.3 coughs/h; P = 0.10). Somnolence was reported by 7 patients on SCH486757, 3 on codeine and 4 on placebo.

The authors concluded that whilst codeine and SCH486757 reduced symptoms similarly, neither were statistically different to placebo. Consideration on the value of patients with subacute cough was also discussed, as symptoms and subjective cough rating declined over the 5 days, therefore subacute cough may not be ideal for future studies of antitussives. The Lifeshirt, consisting of a plethysmograph and throat microphone was also cumbersome and had potential to inhibit patients from their usual daily activities. The study also highlighted the limitations of animal studies where efficacy is evaluated against chemical irritants (capsaicin, citric acid) or mechanical induced cough. The authors consider that the results provide hints of antitussive efficacy, although statistical power was limited due to low numbers of patients and substantial decline in symptoms even on placebo.

[5] Woodcock A, McLeod RL, Sadeh J, Smith JA. The efficacy of a NOP1 agonist (SCH486757) in subacute cough. Lung. 2010 Jan;188 Suppl 1:S47-52. doi: 10.1007/s00408-009-9197-8. PMID: 19937046.

Assessor's comments: the study evaluated codeine as an established antitussive in comparison to a novel NOP1 agonist and placebo. Neither of the two actives showed statistically significant difference to placebo although some improvement was observed. Standard deviations are not reported, therefore whilst the change in median cough score may appear substantial, the range of scores cannot be seen. However, cough scoring was subjective and the validity of the Lifeshirt was questioned in this patient population, as there was potential for false positives when a cough sound is recorded, although may not be indicative of a full cough reflex.

3.3. Efficacy of morphine in cough

The European Respiratory Society provides guidance on the treatment of chronic cough. One treatment option is the use of morphine, supported by a RCT in adults; these data are relevant since codeine is a prodrug of morphine.

Morice et al 2018

Codeine is a prodrug that is metabolised into morphine, subsequently considered to provide the main activity as the potent opioid. Therefore, to circumvent any variability in patient CYP2D6 activity, the authors chose to examine the effects of morphine as an antitussive. In addition, consideration was given to the suitability of subacute cough as a subject for examination as it could resolve without further medical intervention and would introduce reservations on any conclusions.

A RCT was conducted in volunteers with chronic cough of >3 months duration. Patients were randomized into a double-blind placebo controlled crossover study. Patients took 5mg slow release morphine sulphate (MST) twice daily over 4 weeks and 4 weeks of placebo. Patients were required to withhold any other cough remedies. Patients made 3 visits to the clinic separated by 4 week intervals, at which patients filled in the 19 item Leicester cough questionnaire which measures impact on chronic cough and daily living. Improvement in score is indicative of better health. Spirometry with reversibility with 2.5mg salbutamol was performed at the first visit and FEV_1 at each subsequent visit. Citric acid challenge was performed at each visit, and the C_2 and C_5 responses determined (concentration of citric acid required to elicit 2 or 5 coughs per inhalation). Cough severity was rated on a score of 0 – 9 and recorded on a daily record card. Adverse events were enquired after at each visit from a symptom checklist to opiate therapy. Patients after the initial crossover were given the opportunity to take part in an open-label extension study doubling the dose to 10mg MST twice daily if they believed that their cough had not been adequately controlled during the core study. The primary endpoint was change in Leicester Cough Questionnaire (LCQ). The diary data were analysed separately comparing treatment arm with placebo as a baseline reading was not available.

Twenty-seven patients were studied, and cough was productive in 16 patients. The mean LCQ was 12.3 (2.5) at baseline, 13.5 (2.7) on placebo (not significant) and improving to 15.5 (2.7) on morphine ($p < 0.01$ vs. baseline, $p < 0.02$ vs. placebo). Significant improvements were observed in physical, psychological and social subgroups. The daily diary showed a significant reduction in the cough score on morphine (3.4 [1.8], $p < 0.01$) whereas placebo had no effect. There was no difference in the geometric means for the citric acid challenges. At end of study, 18 continued into the open-label extension study and one third increased their dose to 10mg twice daily in the first month, 11% joined this group in the second month and 22% chose to increase the dose in month 3. Ultimately two-thirds chose to increase their dose to 10mg twice daily. For those who opted to stay on 5mg at the end of the

study, the daily cough score had reduced by 2 compared to 0.7 for the others who had opted for increased dose. Patients who had increased their dose showed no significant difference in LCQ with 5mg however significant improvement with 10mg. No patient dropped out because of adverse events, of which the most common was constipation and drowsiness.

The authors noted ease of prescribing of codeine potentially from its non-controlled status, however, therapeutic response is dependent on CYP2D6 activity which is variable. However, the current study showed benefit from treatment with morphine, although there are limitations including the potential for non-complete blindness owing to patient awareness of side effects. Similarly long-term effects were not examined.

Assessor's comments: this study indicates that low-dose morphine is an efficacious antitussive. Codeine is a prodrug of morphine, which is reliant on CYP2D6 for metabolism into morphine. However, CYP2D6 is polymorphic, therefore codeine may be efficacious in patients who are ultra-rapid metabolisers, whilst ineffective in patients who are poor-metabolisers. Previous RCTs have not been able to define CYP2D6 status of the subjects involved, therefore are likely to present a mixed group of patients. The summary of product characteristics (SmPC) for codeine contains information on the percentage of the population who are poor metabolisers or rapid metabolisers, with approximately 7% of Caucasian population presenting as poor-metabolisers, and 3 – 6% rapid metabolisers. Notably, 29% of African/Ethiopian population are ultra-rapid, therefore efficacy may differ according to ethnicity and ultimately the efficacy of codeine as an antitussive.

4. SAFETY

Codeine linctus has been reviewed by CHM (2010) in the treatment of cough in children. The risks associated with the metabolism of codeine and the potential for toxicity in children led to the CHM recommendation that codeine should not be used in patients under the age of 18 years. In 2015 following an article 31 review, the European Pharmacovigilance Risk Assessment committee (PRAC) came to a similar conclusion however, recommended that it could be used in children aged 12 to 18 years without compromised respiratory function. In 2018, the FDA issued a safety statement confirming a change to the label that codeine linctus should not be used in children ≤17 years. Indeed, the WHO removed codeine as an essential medicine for children in 2011. The WHO defines an essential medicine as being " the most efficacious, safe and cost-effective medicines for priority conditions"[6].

As a consequence, there is variability between the MAs. Overall, the indication for the pharmacy product is for 'the relief of an unproductive dry cough'. The posology is 5 -10ml three to four times a day. Codeine is contraindicated in children below the age of 12 years and not recommended for use in children aged 12 years to 18 years with compromised respiratory function.

Opioid toxicity may manifest itself as symptoms of associated with overdose, such as respiratory depression, pinpoint pupils, coma and death. Other side effects are constipation and associated gastrointestinal disorders; dry mouth; psychiatric disorders such as euphoria, dysphoria, confusion; nervous system disorders such as

[6] World Health Organization Model list of Essential Medicines, 21st list, 2019. WHO model list of essential medicines - 22nd list, 2021

dizziness, seizures, addiction, dependence, sleep disturbances; cardiac disorders; muscle rigidity; urinary retention, decreased libido, and skin or sensitivity disorders such as skin rashes, urticaria, pruritus and sweating.

The main risks in adults are linked to the metabolism of codeine, dependence / addiction, and overdose.

4.1. Addiction and Recreational Use

Codeine is an opioid and prone to addiction. The risk of addiction to codeine was reviewed by CHM in 2005, 2009 and 2019. At each stage it has been observed that previous risk minimisation actions have been insufficient to minimise risk and addiction continues to be a problem. Codeine linctus is available as a medicine under the supervision of a pharmacist as it is considered a 'weak' opioid, however, potentially has the unintended consequences of patients misunderstanding of the significance of risks.

It has come to the attention of the MHRA that codeine linctus is being used recreationally to make a drink known as 'Purple Drank', 'Lean', 'Dirty Sprite' or 'Sizzurp' (herein collectively referred to as Purple Drank). Purple Drank is a mix of codeine linctus, promethazine and fizzy drinks, sometimes with boiled sweets to take away the bitterness of the linctus. Codeine provides the euphoria sought by users. Promethazine is added to counteract any sensitivity reactions to codeine however is also a sedative, hence the name 'Lean' as people literally may need to lean on something after it takes its effect. As a recreational drink, people may not be aware of how much they are taking and this can have serious risks, especially if taken with alcohol. Concomitant use with a central nervous system (CNS) depressant, including alcohol, will increase the risk of respiratory depression.

The use of Purple Drank has been popularised through hip hop and Rap music[7] and social media[8,9]. Some prominent rappers have died from overuse and addiction to Purple Drank[10,11]. Whilst this recreational use was initially identified in the US, Purple Drank is relatively easy to make with codeine linctus as it's available without a prescription. Hence this is a safety concern in the UK, especially within the younger population[12] as people are led to believe there are few safety issues. A lethal oral dose is reported to be between 500mg to 1,000mg[13] and a toxic dose is 2.5mg/kg[14]. These figures can also be variable, depending on whether the patient is opioid naïve or has developed tolerance. Given the high profile in the media, there is potential risk of fatalities occurring from the recreational use of Purple Drank, however, no UK deaths have specifically been linked to the abuse of Purple Drank. Fatal overdose from codeine is possible: from 2011-2021 codeine-related deaths in the UK increased from 128 to 200 although there is no information available about what formulation of codeine was involved in these fatal events.[15]

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[7] https://www.popmatters.com/codeine-club-music-sizzurp-lean-2641236442.html
[8] https://www reddit.com/r/codeine/
[9] Cherian *et al* JMIR Public Health Surveill 2018;4(1):e22) doi: 10.2196/publichealth.8144
[10] https://www.theguardian.com/music/2020/jan/22/juice-wrld-death-accidental-overdose-oxycodone-codeine
[11] https://variety.com/2018/music/news/fredo-santana-rapper-dead-dies-1202670978/
[12] Devon parents warned about dangerous Purple Drank craze | Daily Mail Online
[13] What Is A Lethal Dose Of Codeine? - Addiction Resource
[14] Opioids (prescribed to humans) - toxic doses (toxbase.org)
[15] Deaths related to drug poisoning in England and Wales - Office for National Statistics (ons.gov.uk)

Data was obtained from the National Poisons Information Service (NPIS) on the number of calls related to the toxic effects and management of codeine overdose. In 2021, the NPIS received 4 calls related to codeine linctus compared with 873 overall. This may not be the complete number as it is not always possible to determine whether codeine linctus specifically is involved as this is dependent on the level of detail in the individual reports.

Table 1. Calls to the NPIS in relation to codeine

	***2022 (TO 26 MAY)**	**2021**	**2020**	**2019**	**2018**	**2017**
Codeine linctus inc. codeine paediatric linctus, Lean (drug of abuse), Purple Drank (drug of abuse), Sizzurp, Dirty sprite and Pholcodine linctus.	2	4	3	5	3	2
OTC branded (inc. Boots/Superdrug codeine combination products, Panadol + codeine, Cuprofen plus and Benylin codeine)	48	29	32	36	32	32
As above, OTC branded plus co-codamol and codydramol	446	484	451	582	507	568
As above OTC branded plus all products containing codeine or dihydrocodeine	728	873	765	965	844	899

*From 1st January 2022, intentional included intentional therapeutic excess, previously this would have been classed as therapeutic error.

Three Coroners reports under regulation 28 of the Coroners (Investigations) Regulations 2013 to prevent further deaths, have highlighted online purchasing of codeine or opioids. One report of a lady who had died from an overdose involving codeine led to the Coroner to remark on the view of the Lead Controlled Drugs Accountable Officer, NHS England & NHS Improvement (South West) that the status of codeine linctus should be changed to prescription only[16].

Epidemiological data highlighted a heterogeneous diffusion of the misuse of this mixture, which is not exclusively linked to a specific type of user[17]. 'Purple Drank' and 'Lean' is popularised on social media platforms, such as Twitter and Pinterest with some images of the substance[18]. Discussion forum sites dedicated to Purple Drank/lean (r/ukLean on Reddit) discuss all things relating to UK lean (Purple Drank) culture and codeine linctus/syrup[19] including guidance and images. Clothing and merchandise can also be purchased from well-known commercial sites with images

[16] https://www.judiciary.uk/publications/katie-corrigan/
[17] Miuli A, *et al*. "Purple Drank" (Codeine and Promethazine Cough Syrup): A Systematic Review of a Social Phenomenon with Medical Implications. J Psychoactive Drugs. 2020 Nov-Dec;52(5):453-462. doi: 10.1080/02791072.2020.1797250. Epub 2020 Aug 4. PMID: 32748711.
[18] Pinterest
[19] UK Lean Community (reddit.com)

and slogans for Purple Drank appealing to the young adult giving an impression of acceptability.

Figure 2. Images showing ingredients of 'Purple Drank'/'Lean' (colour sometimes dependent on fizzy drink or boiled sweets) and merchandise for purchase (from discussion forum website, commercial websites).

Generally, Purple Drank is made at home in unmeasured amounts of codeine linctus and promethazine, however, is also available ready-mixed to buy on-line, although the quantities of codeine in the drink is unlabelled and unquantified. Websites can be found based in the UK as well as in the US, offering different bottle sizes and flavours of ready mixed Purple Drank concentrate [20]. Rosenberger et al (2021)[21] undertook an analysis of 3 samples of Dirty Sprite (Purple Drank) ordered by German journalists via social media for investigation, with the aim to identify and quantify the drugs present in the preparations. Sample 1 contained 130mg/L codeine, 75mg/L promethazine and 3.4mg/L cocaine; sample 2 contained 74mg/L promethazine and 91 mg/L dihydrocodeine; sample 3 contained 130mg/L codeine and 68 mg/L promethazine. This highlights that mixed preparations can contain additional addictive drugs which can result in a person seeking to buy more and becoming addicted to illicit as well as licit drugs.

4.1.1. Case reports

Three case reports highlight the use of codeine oral solution.

In 1 yellow card case report, the reporter (a consumer) described his 3-year habit of mixing a bottle and half of codeine linctus (900mg) into fizzy drink each day, although he has now stopped this (and he experienced withdrawal symptoms while doing so). He expressed concern that this practice is gloried in rap music, and there are online instructions on how to do this.

[20] Products – LeanUKlabs
[21] Rosenberger W *et al* Drug Test Anal. 2022;14:539–544

A 44 year-old female who became addicted to codeine after drinking one bottle a day for approximately 2 years. The reporter (not the patient) commented that codeine linctus should not be available OTC and there is little help for people with addiction to OTC drugs.

Stewart and McGlen (2019) [22] report a male patient who experienced serious adverse effects after consuming codeine after tampering with codeine-containing products. The patient presented to hospital after misusing codeine by extracting codeine from codeine/paracetamol combination medicines and codeine/ ibuprofen combination medicines. The patient had previously used codeine linctus to support his addiction, however found it increasingly hard to purchase from pharmacies and therefore began to extract codeine from the combination products using cold-water methods found through web pages and on-line forums.

Assessor's comments: there will be significant under-reporting to the yellow card scheme as these cases involve the recreational drink which is an illicit substance. The identification of case reports is also confounded by the multiple names of Purple Drank, therefore unless the reporter is able to positively identify codeine as the potential active substance, it is less likely to be reported.

4.2. Diversion

4.2.1. Reports to MHRA Inspectorate

The MHRA have seen a surge of referrals since 2018, when the phenomena first appeared in the UK and suggest that use in the community is widespread and increasing. Over the past 18 months there have been 50 – 60 referrals (approximately 3 per month). The MHRA have received reports regarding wholesale purchases of codeine linctus and promethazine in increasing amounts indicating over buying malpractice at pharmacy level, for example ordering of over 500 bottles in a single order when the normal quantity per month would be 10 bottles.

Most referrals coming to the MHRA have been for theft or diversion of the constituent products via fraud. As a result, enforcement of the issues is usually referred to the Police, with GPhC tackling the pharmacy overbuying aspect. This has included 'ghost' pharmacists purporting to be ordering for a reputable pharmacy and using the reputable pharmacy details when contacting large legitimate medicine wholesalers.

An example of a recent report concerns a police raid in a London cannabis factory (July 2022) which also located boxes of codeine linctus, promethazine, pregabalin, dihydrocodeine and other mixed medicines. Other examples include attempts to bribe / corrupt staff, organised robberies (involving weapons), and importation from abroad of the unlicenced product.

The MHRA Borderline unit considers the products when mixed have no medicinal use and thus is a substance of abuse[23]. However, the police have limited powers when encountering an individual(s) in possession of large quantities of codeine linctus and promethazine as they are licenced medicines. The police can take action against criminal activity and also have powers under the Psychoactive Substances Act 2016 only when the two active substances are mixed to make Purple Drank. In

[22] Stewart C, McGlen S. Pharmacy staff should be aware of drug misusers' methods of extracting opioids from OTC products. Clinical Pharmacist. 2019;11(6) on 02-Jul-2019
[23] MHRA Intelligence Unit the Purple Drank Phenomena (Official Sensitive)

the pharmacy a 200ml bottle costs very little, however sells at greatly inflated prices on-line (£70 – £120), therefore reflecting demand and the lucrative business.

The role of the MHRA has been collection and dissemination of incidents and intelligence, obtaining sales data for the products from wholesalers at the request of GPhC and keeping relevant parties educated and informed.

The MHRA borderline unit have made a number of presentations raising the issue via the inspectorate blog and through webinars, however this remains a growing safety concern, not only to the patient / user, but also to the pharmacist and staff at wholesalers.

4.2.2. Roundtable September 2022

The MHRA held a roundtable consisting of colleagues from a number of government departments in the UK, the Healthcare Distribution Association (HDA), The National Crime Agency (NCA), Advisory Council on the Misuse of Drugs (ACMD), General Medical Council, the General Pharmaceutical Council (GPhC), and the Royal Pharmaceutical Society (annex II). The HDA have informed the MHRA that they now have a cap of 12 bottles per order. The GPhC reported that they had taken action against 6 pharmacies in 2020, regarding the sales of codeine linctus. Since then the GPhC reported taking action against 43 pharmacy premises[24] and informed the roundtable that they have now taken action against 45 pharmacies, of which 27 have also stopped selling promethazine.

The roundtable discussed the concerns of HDA members being held at knife point, however the MHRA highlighted the limited powers of the police to act on reported cases where people were found in possession of multiple bottles of authorised medicines. Therefore, the potential of making a Purple Drank a new psychoactive substance under the Psychoactive Substance Act 2016 was discussed. Consideration was also given to the lack of police awareness as many incidents were unreported. The NCA highlighted action undertaken in Surrey[25].

Overall, it was agreed that the challenge to protect patient safety is multifaceted and requires action from across the system, covering best practice, sales, delivery quotas, legal status as defined in the Human Medicines Regulations 2012, potential for categorisation of the combination of codeine and promethazine as a psychoactive substance within the Psychoactive Substances Act 2016, and public education (minutes annex II).

5. SALES OF CODEINE

Marketing Authorisation Holders (MAHs) were asked for their sales data to provide an estimation of patient exposure. This includes sales to wholesalers. Overall, the main sales are of the 200ml bottle and overall have been decreasing over the past 5 years from a total of 367,824 bottles in 2018 to 267,228 bottles in 2021 whereas sales of the 2 litre bottles reduced from 11,562 bottles to 9,348 bottles.

[24] www.pharmacyregulation.org/regulate/article/focus-monitoring-sale-and-supply-medicines-subject-abuse-or-misuse
[25] Pharmacy worker and drug dealer sentenced for large-scale drug supply across London | Surrey Police

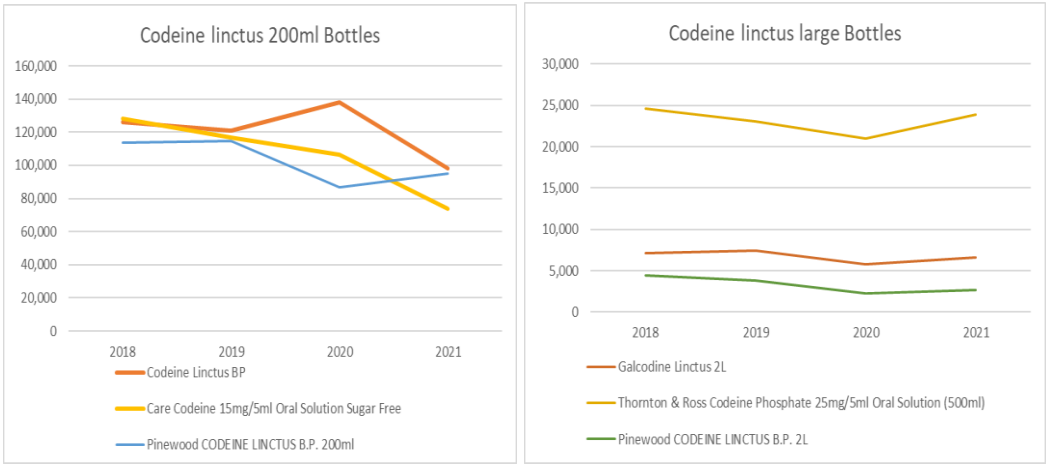

Figure 3. UK sales of bottles of codeine linctus 15mg/5ml from the MAHs since 2018. Data provided for 2017 was incomplete.

Data was obtained from IQVIA and IQVIA MIDAS providing information on sell-in data to the retail sector and dispensing data. Sell-in data between Dec 2019 and Nov 2020 indicated a decline in sales in the first half, although the impact of the pandemic could not be ruled out.

Table 2. Volume Sell-In data for OTC codeine linctus/syrup products (IQVIA MIDAS, OTC Sell-In Data, 12/2019-11/2020)

Year - Month	TOTAL	Retail Pharmacies	Dispensing Practices	Unspecified
2019 - 12	31835	29390	1062	1383
2020 - 1	30896	28526	1069	1301
2020 - 2	22697	20795	691	1211
2020 - 3	29226	26771	1010	1445
2020 - 4	22054	20238	776	1040
2020 - 5	15942	14531	438	973
2020 - 6	22307	20554	533	1220
2020 - 7	22791	20783	485	1523
2020 - 8	21439	19969	410	1060
2020 - 9	22770	21229	570	971
2020 - 10	21005	19729	596	680
2020 - 11	20026	19079	521	426

Dispensing data by prescription in UK retail and hospital pharmacies again showed an overall decline from Jan 2016 to Dec 2020.

Table 3: Volume of dispensed products (as pre-specified), in retail and hospital pharmacies. (*Data Source: IQVIA MIDAS, 2016 – 2020*)

	2016	2017	2018	2019	2020
HOSPITAL	32,170	30,672	32,357	32,236	25,217
RETAIL	198,175	169,188	147,163	137,066	114,921
TOTAL	230,345	199,860	179,520	169,302	140,138

Using the overlapping data, an estimation is possible of the OTC sales of codeine linctus in 2020.

Table 4. Estimations of the Volume of Product available for OTC sales

Data Source	2020 Q1	2020 Q2	2020 Q3
Retail Sell-in	82,819	60,303	67,000
Dispensing	35,462	27,477	24,843
Est. OTC	47,357	32,826	42,157
% OTC	57.18%	54.44%	62.92%

This data would indicate that prescriptions decreased during 2020 and non-prescription dispensing increased. This may again be indicative of the effect of the pandemic and the period of lock-down. In 2021 (updated 09/07/2022), NICE produced rapid guidance on the treatment and management of symptoms related to Covid-19 and cough if distressing, recommending the prescription of codeine in adults[26].

6. INTERNATIONAL REGULATORY ACTIVITY

In 2016, the National Agency for the Safety of Medicines (ANSM) in France issued a warning note to pharmacists and doctors[27] which urged them to make sure patients do not have a history of drug abuse and addiction before prescribing cough syrup. Since July 2017, all codeine-containing medicines have been available only on prescription in France and all oral formulations of promethazine have required a prescription since Jan 2020[28].

Codeine linctus was recalled and banned from sale in Nigeria following reports of addiction associated with illegal sales to drug dealers. Ghana followed suit, banning sales, production and importation of codeine linctus after discovering significant levels of consumption[29].

7. TERMS OF REGULATION

Criteria for classification are set out in Regulation 62 of the Human Medicines Regulations 2012. Regulation 62(3) identify that prescription control is required for medicines which meet the following criteria:

> *(a) is likely to present a direct or indirect danger to human health, even when used correctly, if used without the supervision of a doctor or dentist;*
>
> *(b) is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health;*
>
> *(c) contains substances, or preparations of substances, of which the activity requires, or the side effects require, further investigation; or*

[26] COVID-19 rapid guideline: Managing Covid-19
[27] (vice.com)
[28] Order of January 21, 2020 relating to classification on the lists of poisonous substances
[29] How to halt a cough-syrup addiction August 2018

(d) is normally prescribed by a doctor or dentist for parenteral administration.

Assessor's comments: This assessment is directed at the first three of these criteria; the last is not relevant since the product is not to be administered parenterally.

The Human Medicines Regulations (62(3)) also stipulate:

(4) In deciding whether paragraph (3) applies to a product, the licensing authority must take into account whether the product—

(c) is likely, if incorrectly used—

(i) to present a substantial risk of medicinal abuse,

(ii) to lead to addiction, or

(iii) to be used for illegal purposes;

(d) contains a substance that, by reason of its novelty or properties, might fall within paragraph (c), but as to which there is insufficient information available to determine whether it does so fall;

It is also stated (Regulation 62(2)) that:

Exemptions from prescription control may be made having regard to:
(a) the maximum single dose;
(b) the maximum daily dose;
(c) the strength of the product;
(d) its pharmaceutical form;
(e) its packaging; or
(f) such other circumstances relating to its use as may be specified in the determination.

8. PRODUCT INFORMATION

8.1. Product name

Codeine oral solutions are available under the trade names, Codeine linctus BP, Bells healthcare codeine linctus 15mg/5ml oral solution, Care codeine 15mg/5ml oral solution, Pulmo Bailly, Thornton & Ross codeine phosphate 25mg/5ml oral solution, and Co-codamol 30mg/500mg/5ml oral solution. The latter two are only available with prescription, whereas the lower strength solutions are available under the supervision of a pharmacist.

Pulmo Baily is not currently marketed, and the MA is due to expire in December 2022.

Assessor's comments: all products should include the amount of codeine contained in the product name in line with Quality Review of Documents (QRD) guidelines regarding the SmPC 2009. It is not consistently displayed, and therefore patients are unaware as to how much codeine they are consuming (annex I).

8.2. Pack size

Codeine linctus is currently marketed in bottles containing 200ml, 500ml, and 2L. Codeine linctus is also authorised in bottles of 1L and lower sizes, of 90ml, 100ml and 125ml, however, these are not marketed. Whilst there are restrictions in pack sizes for codeine tablets, there are currently no restrictions on the pack size for pharmacy availability of the codeine linctus.

Assessor's comments: Current sales are highest for the lowest marketed size (200ml). Only 3 MAHs with codeine linctus as pharmacy availability have authorised bottle sizes less than 200ml, one of which is Pulmo Baily (where the MA is due to expire) and this contains codeine 7.0mg/5ml plus 75mg/5ml guaiacol.

Current posology for most codeine linctus products is 5ml which may be repeated after 4 hours if required with no more than 4 doses in 24 hours (max 20ml or 60mg codeine). However, the posology for PL 04917/0001 (codeine linctus) is 5ml to 10ml, 3 to 4 times daily (max 40ml or 120mg). Therefore, there is inconsistency which has potential for overuse of the product. It would be beneficial to achieve consistency to prevent misunderstanding of the safety of codeine linctus.

A consideration of the maximum duration of use before further advice should be sought from a physician would have an impact on the suitability of pack size available from a pharmacy. Co-codamol tablets from the pharmacy are recommended for a maximum duration of 3 days use, after which advice should be sought from the healthcare professional; therefore it would seem reasonable that the same advice is applied to codeine linctus.

A pack size of 100ml would be more than sufficient for 3 days use at the posology of 5ml per dose. However, none of the MAHs are currently marketing these pack sizes, and any requirement to market a smaller bottle size of 100ml would mean a significant delay in these bottles appearing on the shelves even if the MAH was willing to launch a smaller bottle size onto the market.

A co-codamol oral solution also has an authorised pack size of 150ml, although regardless of pack size, this is a prescription only product.

8.3. Product warnings and precautions

Codeine linctus is not currently recommended for use in children between the ages of 12 and 18 years with compromised respiratory function and is contraindicated in children aged under 12 years. Codeine linctus is also contraindicated in;

- patients for whom it is known they are CYP2D6 ultra-rapid metabolisers
- breastfeeding
- liver disease due to potential drug accumulation
- respiratory depression
- in patients with raised intracranial pressure
- paralytic ileus
- during asthma attack

Assessor's comments: The licences of codeine linctus do not currently include the contraindication for children under 18 who undergo tonsillectomy and or adenoidectomy for obstructive sleep apnoea which is present in all the other formulations for codeine indicated for pain. However, codeine linctus is not authorised for pain, and only one licence authorises use in children between the ages of 12 and 18 years, although not recommended in patients with compromised respiratory function. This follows PRAC recommendations following an article 31

referral (2015) as the risks associated with the metabolism of codeine into morphine can be significant for children. For consistency and the prevention of misunderstanding, use should be for adults only aged 18 years and over as recommended by CHM 2010 Codeine-containing liquid over-the-counter medicines. - GOV.UK (www.gov.uk). In 2018, the FDA also issued a safety communication announcing that codeine should not be used in children aged 0 to 17 years FDA Drug Safety Communication: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older | FDA.

As noted in comments above, co-codamol tablets which contain codeine and paracetamol have a limitation on duration of use, for 3 days, after which the patient should seek the advice of a physician. Therefore, it would be reasonable that codeine linctus has the same recommendation, although for co-codamol, the limitation is based on applied risk minimisation measures for both actives.

In 2019, CHM recommended that labels should contain the warning “can cause addition, contains opioid”, and the Summary of Product Characteristics (SmPCs) and patient leaflets of prescribed codeine should contain consistent warnings and recommendations with all other opioids. Current warnings for OTC codeine linctus are in line with CHM 2009 recommendations to warn against use if the patient has a history of addiction to codeine or morphine, although there is no information concerning the symptoms of addiction. Therefore this information should be included in line with POM codeine.

9. DISCUSSION

Codeine is a prodrug which is metabolised into morphine via the polymorphic enzyme, CYP2D6. As a consequentially its efficacy is variable as it is dependent on the individual’s enzyme active status which can vary with ethnicity. Codeine is widely recognised medicine used in the treatment of pain and as an antitussive. Codeine linctus is only authorised as an antitussive in adults and adolescents over the age of 12 years without respiratory disorders. There is little clinical evidence to support efficacy as an antitussive in the treatment of acute or subacute cough, although some evidence for the metabolite, morphine, in the treatment of chronic cough. As a medicine with a well-established efficacy and safety profile, codeine linctus does not meet the following POM criterion:

> *(c) contains substances, or preparations of substances, of which the activity requires, or the side effects require, further investigation*

As an opioid, there is a risk of addiction with overuse. The risks of opioid toxicity can vary dependent upon the patients’ previous usage of opioids, as patients can develop tolerance over time.

Codeine linctus has been identified as a component of a recreational drink with multiple names including ‘Purple Drank’, Lean’ ‘Sizzurp’, ‘Dirty Sprite’ and is also identified by logos and emojis. The drink has been popularised through the media and music culture to young adults and adolescents. Purple Drank is available to buy ready mixed or in kits through on-line websites and is also advertised on clothing and other merchandise giving an impression of acceptable safety. Purple Drank will give the user a feeling of euphoria and sedation. However, Purple Drank is a mix of codeine and promethazine with a fizzy drink and is generally home made in unmeasured amounts with a risk that the user will overdose on codeine. Its toxicity

with risks of sedation and respiratory depression may be exacerbated by the concomitant use of alcohol.

The death of prominent music artists highlighted the risks of addiction associated with Purple Drank. Whilst codeine might be viewed as a 'weak' opioid, it is known for its addiction potential and has been hypothesised to act as a gateway to additional substance abuse[30]. The acquisition of ready mixed 'dirty sprite' (Purple Drank) has also identified the introduction of additional addictive licit and illicit drugs. The death of the hip hop artist 'DJ Screw' following an addiction to Purple Drank, was also linked with the use of Valium and phencyclidine, although it is unknown whether Purple Drank was the initiator of his addiction. However, several other Rap artists linked 'sipping codeine' in their music with heart attacks, seizures and withdrawal symptoms[31]. Whilst this may be considered a problem in the US, the media and on-line purchasing is not constrained by borders and is a safety concern when popularised through UK artists into use by students and young adults[32].

It is difficult to determine the total background use, incidence of adverse reports, degree of harm, or fatalities from the recreational use of Purple Drank, as it has many names, is identified through logos and emojis and its components are frequently obtained illegally. Similarly, adverse events related to the use of Purple Drank will be significantly under-reported reported to the yellow card scheme as it is non-medical use. Although one literature report of a man who began to extract codeine for combination medicines owing to lack of access to the linctus, shows an unintentional consequence of earlier regulatory actions. However, recreational activity has prompted safety warnings, both within local regions of concern (schools), police notices and generally through professional healthcare best practice guidance.

In Birmingham for example, South Yardley Neighbourhood Team sent letters to local pharmacies warning them of illicit substance 'Lean'.[33] Police forces have released statements regarding its distribution, especially to younger people. Staffordshire police have advised parents to keep their children aware of the risk.[34] Charities are beginning to raise more awareness about the effects of Purple Drank/Lean, as use of it in the UK has been particularly linked to young people.[35] In 2018, the UK Association for Forensic nurses and Paramedics also published an alert raising awareness of the drink with their members[36].

It could be argued that the acquisition of codeine linctus through criminal activity and diversion can also have an indirect effect on human health of pharmacists and warehouse suppliers. However, it is unlikely to have a direct effect on human health if used correctly, therefore codeine linctus does not meet the first POM criterion:

> *a) is likely to present a direct or indirect danger to human health, even when used correctly, if used without the supervision of a doctor or dentist;*

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[30] Peters Jr RJ, Kelder SH, Markham CM, Yacoubian Jr GS, Peters LA, Ellis A. Beliefs and social norms about codeine and promethazine hydrochloride cough syrup (CPHCS) onset and perceived addiction among urban Houstonian adolescents: an addiction trend in the city of lean. J Drug Educ 2003;33(4):415-425. [doi: 10.2190/NXJ6-U60J-XTY0-09MP]

[31] Codeine Club Music: 10 Sizzurp Rappers and Their Lean Lyrics | PopMatters

[32] Lethal cough syrup drug blamed for Ariana Grande's ex-boyfriend rapper Mac Miller's death is sweeping the UK | The Sun

[33] Police warning over 'lethal drug' Purple Drank (birminghammail.co.uk)

[34] (thomasalleynes.uk)

[35] Lean Infosheet(thedrugswheel.com)

[36] ALERT | 'Purple Drank' – UKAFN.org

However, by way of localised intense activity and promotion of use, evidence would suggest that codeine linctus potentially meets the second POM criterion in terms of causing harm if used incorrectly;

> *(b) is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health;*

Arguably the scale of the 'Purple Drank' problem, harm arising from this, diversion and criminal activity to support it use is difficult to quantify, which calls into question whether the product is "frequently and to a very wide extent used incorrectly". However, it is important to take into account that the Regulation 62(4) applies in relation to codeine linctus:

(4) In deciding whether paragraph (3) applies to a product, the licensing authority must take into account whether the product—

> *(c) is likely, if incorrectly used—*
>
> *(i) to present a substantial risk of medicinal abuse,*
>
> *(ii) to lead to addiction, or*
>
> *(iii) to be used for illegal purposes*
>
> *(d) contains a substance that, by reason of its novelty or properties, might fall within paragraph (c), but as to which there is insufficient information available to determine whether it does so fall;*

Respondents to a poll undertaken by the publication, Chemist and Druggist, indicated that 70% of pharmacy professionals considered that codeine linctus should be reclassified as POM[37]. Moving codeine linctus to POM would not remove the potential for recreational use, however, would introduce a further barrier for the purchaser to surpass. In addition, a prescription would specify the amount of codeine linctus for supply to the patient and would also enable the pharmacist to keep better records on sales. Prescription would also enable the pharmacist to monitor the patient's usage through their summary care record (SCR).

There is little evidence to support efficacy in acute or subacute cough, a condition which is self-limiting. There are alternative OTC cough medicines including syrups and lozenges containing e.g. glycerol, honey and lemon or guaifenesin dependent on the type of cough. However, there is evidence to support efficacy in patients with chronic cough, a condition which is likely to be monitored with the supervision of a healthcare professional (HCP).

In 2021, a study of the North West London dataset (Discover) encompassing information from primary and secondary care, indicated that approximately 2% of patients were diagnosed with chronic cough, mainly in women and aged between 65 and 74 years. Only 1.4% of individuals were prescribed morphine. However, chronic cough is associated with a number of background comorbidities, including asthma, chronic obstructive pulmonary disease, and smoking[38] and can be distressing for the

[37] C+D readers want codeine linctus to switch from P to POM, poll shows :: C+D (chemistanddruggist.co.uk)

[38] Hull JH, Langerman H, Ul-Haq Z, Kamalati T, Lucas A, Levy ML. Burden and impact of chronic cough in UK primary care: a dataset analysis. BMJ Open. 2021 Dec 17;11(12):e054832. doi: 10.1136/bmjopen-2021-054832. PMID: 34921086; PMCID: PMC8685971.

patient. Some comorbidities may need diagnosis and supervision of care through GPs, however, others such as smoking cessation can be aided with the support of pharmacists, who can also give advice on OTC cough medicines.

Codeine linctus could remain a 'P' medicine with improved product information and strict controls on sales to minimise the risks of misuse and diversion, involving additional training for pharmacists and pharmacy staff. The Prescription only Medicines (Human Use) Order 1997, Schedule 2, currently states that codeine may be exempt from prescription at a maximum single dose equivalent to 20mg codeine monohydrate. Therefore, a restriction could be placed on codeine linctus for a maximum single dose of 5ml (15mg) and the posology for a single dose of 10ml (30mg) removed as this exceeds the 20mg limit and would be considered prescription only. In 2007 CHM recommended several risk minimisation measures to prevent the misuse of pseudoephedrine which was identified to be used to make methylamphetamine ('crystal meth') with ephedrine for recreational use[39]. These measures also included restrictions on the sales of pseudoephedrine to the public, prohibiting promotions of multiple packs, restriction to one pack per transaction, restriction on pack sizes (to 720mg pseudoephedrine in total per pack) and improved record keeping. A reduction in the pack size of codeine linctus to 100ml, would enable 3 – 5 days use at the lower single dose of 5ml (15mg), to be taken a maximum of four times a day.

10. CONCLUSION

Codeine linctus is a cough medicine authorised in the treatment of unproductive cough, however there are growing reports diversion and criminal activity through Police referrals, enforcement actions by the GPhC and concern raised from the HDA over the safety of their members.

Recreational use by adolescents and young adults by mixing with promethazine and fizzy drinks to make the drink 'Purple Drank' is a safety concern as there is a risk of overdose and addiction.

There is a lack of evidence of significant harm in the UK (lack of yellow cards and calls to NPIS), however this is likely due to the illicit use of the medicine, especially in this young population, therefore will be subject to significant under-reporting. However, there are anecdotal reports of serious events (fatalities) reported in the US.

Regulatory activity has been undertaken in other countries (France, Nigeria, Ghana) consisting of reclassification or suspension of the MA, specifically to address the arising problem of Purple Drank and the adverse effects resulting from the overuse of codeine linctus.

Taking into account the potential for misuse, addiction, and use for illegal purposes, the POM criteria; *(b) is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health;* may be met. However, given that licit patient exposure to codeine linctus is likely to be low, alternative activities could be considered to tighten the control of sales, improve product information and education for healthcare professionals, could be considered. Therefore, a period of public consultation would be useful to obtain views on the

[39] MHRA public Assessment Report July 2009 Controlling the risk of misuse of medicines containing pseudoephedrine and ephedrine

merits of the proposals and any other views from healthcare professionals and the general public.

11. ADVICE SOUGHT

Advice is sought from the Commission whether codeine linctus meets the second criterion for legal classification of Prescription Only Medicine as set out in Regulation 62(3) of the Human Medicines Regulations 2012:

- "*is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health"*.

- Taking into consideration:

  (c) is likely, if incorrectly used—

  (i) to present a substantial risk of medicinal abuse,

  (ii) to lead to addiction, or

  (iii) to be used for illegal purposes

  (d) contains a substance that, by reason of its novelty or properties, might fall within paragraph (c), but as to which there is insufficient information available to determine whether it does so fall;

Alternatively, may safely be sold under the supervision of a pharmacist under some or all of the following conditions:

- Reflection of the concentration of codeine in the product name,
- Maximum single dose of 5ml (15mg)
- Maximum daily dose of 20ml (60mg)
- Maximum strength 15mg/5ml
- Contraindication for use in children and adolescents under the age of 18,
- Recommendation to limit duration of use to 3 - 5 days,
- Maximum pack size of 100ml

In terms of sales, additional measures could be taken to improve awareness in the pharmacy profession advising to:

- Alert to safety concerns relating to recreational use, addiction and diversion
- Limit sale to 1 bottle only in any one purchase,
- Prohibit sales of promethazine in the same transaction
- Keep out of sight at the pharmacy
- Require personal pharmacist supervision of sale/supply of codeine linctus

ANNEX I. List of Authorised oral codeine solutions authorised for the treatment of cough.

PL number	Product Name	Active	Legal status	Pack size
PL 12965/0009	Codeine linctus bp	Codeine 15mg/5ml	P	200ml
PL 03105/0063	Bells healthcare codeine linctus bp codeine phosphate 15 mg per 5 ml oral solution	Codeine 15mg/5ml	P	200ml *100ml* 500ml**
PL 00240/0099	Care codeine 15mg/5ml oral solution sugar free	Codeine 15mg/5ml	P	200ml, 2000ml
PL 04917/0001	Codeine linctus b.p.	Codeine 15mg/5ml	P	200ml, 2000ml *125ml* 100ml* *1000ml**
PL 52731/0008	Pulmo Bailly	Codeine 7mg/5ml Guaiacol 75mg/5ml	P	*90ml**
PL 00240/6213R	Thornton & ross codeine phosphate 25mg/5ml oral solution	Codeine 25mg/5ml	POM	500ml
PL 29831/0590	Co-codamol 30mg/500mg/5ml oral solution	Codeine 30mg/5ml Paracetamol 500mg/5ml	POM	*150ml* 200ml* *500ml**

*not marketed

ANNEX II. Minutes of Codeine linctus Roundtable August 2022.

Medicines & Healthcare products Regulatory Agency

Minutes

Title of meeting	Codeine Linctus Roundtable		**Time**
Date	25 August 2022		10:00
Venue	Virtual		
Chair	Alison Cave	MHRA	
Attendees	[redacted]	MHRA MHRA MHRA MHRA	
	[redacted]	DHSC Department of Health and Social Care Department of Health and Social Care SPPG Medicines Regulatory Group, Department of Health NI Healthcare Distribution Association AAH Pharmaceuticals Limited National Crime Agency ACMD General Medical Council Royal Pharmaceutical Society General Pharmaceutical Council Scottish Government	
Observer	[redacted]	MHRA MHRA MHRA	
Apologies	[redacted]	NHS England	

1) Attendees of the roundtable were reminded that the workshop had been convened to discuss the growing concern over diversion and misuse of codeine linctus and promethazine in relation to the recreational drink ‘Purple Drank’ or ‘Lean’ which is made from a mixture of these medicines, together with fizzy drinks and boiled sweets.

2) Attendees at the roundtable events noted the following background information presented by the MHRA:

    a) The MHRA noted that it has been reported that codeine linctus has also been mixed with other medicines such as benzodiazepines and alcohol in the preparation of these drinks. Social media platforms such as Reddit and TikTok also show how easy it is to make.

    b) Codeine is an opioid which may have euphoric effects, whereas promethazine is a sedating antihistamine which will prevent some of the itching that people may experience when taking high doses of codeine. Codeine linctus and promethazine are pharmacy medicines, available without prescription under the supervision of a pharmacist. There are no licensed combinations of codeine and promethazine, therefore the combination of these substances in this drink is not considered a medicine.

    c) There is concern that the use of codeine linctus and promethazine to make this drink could be increasing in the UK, although the extent of this is unknown. There are no reported deaths in the UK related to Purple Drank (Lean) to date, although deaths have been reported in the US. The use of Purple Drank has been promoted through the music scene, in soul music, rap and hip-hop music, and has been associated with the deaths of some prominent rappers.

    d) The extent of potential harm is difficult to quantify due to the illicit nature of Purple Drank. The MHRA has received very few Yellow Cards for codeine linctus describing problems with dependence. The National Poisons Information Service receives around 3-5 calls in relation to codeine linctus per year, and around 700 - 800 calls per year for codeine overall. Data from the Office for National Statistics (ONS) suggest there were approximately 200 codeine-related deaths in 2021 in England and Wales (although the level of detail is limited to that presented on the death certificate and details of the formulation in these cases is unknown).

    e) There is increasing criminal activity to divert codeine linctus and promethazine from warehouses to sell on-line and on the black market, where it is sold for £70 a bottle. Codeine linctus is available from legitimate websites at the normal price of £3.50 a bottle and can also be sold ready mixed with promethazine on illegal websites at much higher prices. The driver for the diversion is therefore the potential for a large mark-up in price and therefore is a lucrative business. The average quantity of codeine linctus ordered by pharmacies is approximately 10 bottles per month, but the MHRA have received reports of pharmacies who have over-ordered of up to 500 bottles.

f) Codeine is a schedule 5 drug under the Misuse of Drugs Regulations 2001 and a class B drug under the Misuse of Drugs Act 1971. Because the concentration of codeine (per single dose) in codeine linctus is low, it is permitted to be sold as a pharmacy medicine.

g) Other countries have taken action to control the sale of codeine. In February 2018, codeine was reclassified as prescription only in Australia. In the US there are also strict controls including prescription status and change to Schedule III by the Drug enforcement administration.

h) The MHRA regularly engage with the police regarding the issue of Purple Drank through the Controlled Drugs Liaison Officers network. The MHRA have been receiving referrals from law enforcement and from wholesalers in relation to codeine linctus. There are examples of ghost purchases, bribery, theft and robberies, therefore there is also a risk to members of the public and staff at warehouses. It is an increasing issue for the police who currently have limited powers when faced with a person in possession of multiple bottles of the medicine, as no crime has been committed in this scenario. The MHRA also have reports from the border force of large imports of unlicenced products from abroad.

i) The MHRA have received sales information for codeine linctus directly from the marketing authorisation holders. Sales have been decreasing over the last 5 years, however the main bottle size sold is 200ml. Sales of other sizes of 500ml, 1L and 2L are very low in comparison. It was noted that pharmacies have kept the 1 L and 2L bottles in stock to dispense against prescriptions, although this is very rare. Larger bottles may also be held in hospitals and nursing homes.

j) The MHRA are in discussion with the General Pharmaceutical Council (GPhC) and the Healthcare Distribution Agency (HDA) who have created a blog about Purple Drank to educate people about it and raise the issue in the industry. The MHRA also undertake GDP inspections of wholesalers and take action against companies where over-ordering is taking place. Wholesalers also have a requirement to monitor transactions and investigate irregularity and report to the MHRA.

3) The following information was shared by HDA and GPhC:

a) The GPhC has undertaken 21 webinars to local firms and committees over the last two years of the risks, enforcement and information gained and has also taken action against 45 pharmacies. Of those, 27 have stopped selling promethazine as well.

b) Pharmacist’s experience is that these products were only requested by repeat users, and generally pharmacists will keep the products behind the counter. Some pharmacists will keep codeine linctus out of sight and only dispense against a prescription. However, while some people requesting codeine linctus can be well behaved and believable, others can be aggressive, and may target extended hour pharmacies or when there is a changeover of staff. Some pharmacies have felt intimidated and pressured into making the sale.

c) The HDA have set tight controls on sales of codeine linctus to pharmacists from warehouses with a cap of 12 standard-size bottles for pharmacy supply and a cap of two of the larger 2 litre bottles. However, many thousands of orders have been attempted of larger amounts of bottles than the cap will allow. The problem areas tend to be city based, within London, North London, Essex border, Glasgow, Birmingham and Manchester. It was not considered that a reduction in the pack size would help as the main sales are the 200ml bottles. The HDA also have an enforcement group and will set quotas on other medicines of concern.

4) The roundtable considered that pharmacists required more education, and that information should be shared between pharmacies in their local area regarding people who are generally known as regular users and who may be trawling between the pharmacies for the linctus.

5) The roundtable agreed that there needs to be more joined up communication between the pharmacies and between wholesalers and other agencies. There are approximately 1900 warehouses in the UK of different sizes and the criminals now tend to target those which are not members of HDA.

6) The roundtable briefly discussed the inclusion of promethazine:

    a) The MHRA has not to date explored the risks associated with promethazine although did inform the roundtable of action taken in France, where codeine was reclassified to prescription only in 2017 followed by promethazine in 2020 on the basis of abuse together with codeine.

    b) The HDA also have imposed quotas on the number of bottles of promethazine liquid sold and have spoken to some pharmacies who have ordered large quantities and who are unaware of the risks. However the HDA noted promethazine is not a scheduled drug therefore there is a different level of risk.

7) In discussion of actions to reduce the criminal threat, the MHRA highlighted that at the current time there is a voluntary agreement with retailers to prevent the sales of more than 2 packs of analgesics, however codeine is not specifically mentioned, and codeine linctus is not authorised for analgesia. There is guidance discouraging volume sales promotions of codeine. There is no legal restriction on the maximum pack size, although the main sales of codeine linctus are currently the smallest marketed size of 200ml.

8) The roundtable commented that a reclassification of codeine to POM would give pharmacists some protection from junior members of criminal gangs, although this would not reduce the abuse demand. It was noted that there may be a shift towards other codeine containing soluble drugs, for example co-codamol. However, pack sizes, greater than 32 tablets including effervescent codeine formulations are only available on prescription.

9) The roundtable commented that they did not know the extent of the problem, nor the impact on actual users, and that action needs to be risk proportionate. The scale of the

problem is unknown as Purple Drank also has several names and on social media platforms may also be referred to by use of an emoji, hence finding data is problematic. Some work was undertaken in NI to inform pharmacists of issues related to abuse of codeine and promethazine which pharmacists found helpful. Therefore education for pharmacists, young people, and the police is key.

10) The roundtable discussed the potential for the combination of codeine and promethazine, to be classified as a new psychoactive substance but noted this would need to be discussed at a subgroup of the Advisory Council on the Misuse of Drugs (ACMD). While, the Psychoactive Substances Act applies to an amount of single drug entities, Purple Drank is a combination of products, and it is recognised that the use of drug combinations are common practice for addicts.

11) The roundtable also noted the large amount of merchandise available to buy promoting purple drank, ‘codein’ or ‘lean’ on retail online websites and were concerned that they promote legitimate use and safe use.

12) The roundtable recognised that there were two groups of people who may misuse codeine linctus: the legitimate patient who may inadvertently become addicted; and the recreational user. The MHRA would take the proposal for reclassification to public consultation, which would also set out other risk minimisation options including keeping codeine linctus out of sight behind the counter and restricting the volume of sales per person. However the MHRA have received many media enquiries over the last 2 years requesting reclassification. Therefore the challenge to protect patient safety and reduce the risk of addiction to (and harm from) Purple Drank is multifaceted and requires action from across the system, covering best practice, sales, delivery quotas, legal status as defined in the Human Medicines Regulations, categorisation of the combination of codeine and promethazine as a psychoactive substance within the Psychoactive Substances Act, and public education.

13) It was agreed that a number of actions would be circulated after the meeting for attendees of the roundtable to take forward.