Medicines & Healthcare products Regulatory Agency

Codeine linctus (codeine oral solutions): Proposal to reclassify to prescription only

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

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Contents

Plain Language Summary

Key messages:

Codeine linctus (also known as codeine oral solution) is used in the treatment of dry cough in adults and should not be used in children aged 12 years to 18 years of age with breathing difficulties. Codeine is an opioid medicine and is addictive. Evidence is limited that codeine linctus is effective in the treatment of short-term cough but may be effective in the treatment of long-term cough (lasting over 8 weeks).

Codeine linctus will now only be available on prescription following assessment with a healthcare professional. This action is being taken to reduce the risk of addiction or overdose. Alternative non-prescription cough medicines are available for short-term cough to sooth an irritated throat, including honey and lemon mixtures and cough suppressants. Patients can speak to a pharmacist for advice.

Patients will still be able to access codeine linctus with a prescription from a qualified healthcare professional. This will ensure that the medicine is used safely and appropriately under medical supervision.

Introduction

This report reviews the benefits and risks of codeine oral solutions (herein referred to as codeine linctus) and the responses to the public consultation on the proposal for a change in the supply of codeine linctus from a pharmacy medicine (P) to a prescription only medicine (POM).

More information about this medicine

Codeine linctus is indicated for the treatment of dry unproductive cough in adults and children aged over 12 years of age without difficulties in breathing.

Codeine linctus has been used as a cough medicine for many years, although the evidence for effectiveness in short-term cough is limited.

Codeine linctus is available from the pharmacy as oral solutions which contain codeine either at a strength of 15mg/ml in bottles containing 200ml or 7mg/5ml in bottles containing 90ml (currently not marketed*), although much larger bottles are available for pharmacists so that they can provide measured amounts to patients. The following table lists the currently authorised codeine linctus medicines.

Product names	Licence holders
Codeine Linctus BP	LCM Limited
	Pinewood Laboratories Limited
Bells Healthcare Codeine Linctus 15mg/5ml Oral Solution	Bell Sons & Company (Druggists) Limited
Care Codeine 15mg/5ml Oral Solution Sugar Free, Galcodine Linctus	Thornton & Ross Limited
Pulmo Bailly*	Dendron Brands Limited

Reasons for the latest review and information considered

There is limited robust evidence of the effectiveness of codeine linctus in the treatment of acute (short-term) cough, although there is some evidence of effectiveness in chronic (long-term) cough which lasts longer than 8 weeks.

Over recent years there have been increasing reports that the combination of codeine linctus (an oral solution), promethazine (an antihistamine) and fizzy drinks is being used to make the recreational drink known as ‘Purple Drank’, ‘Lean’, ‘Dirty Sprite’ or ‘Sizzurp’ (herein collectively referred to as Purple Drank). The promotion of Purple Drank through the media, and recreational use in young adults in the UK has prompted warnings in the UK concerning the risks associated with Purple Drank, including dependence, addiction, and the risk of overdose (for example Staffordshire police alert). Pharmacists also reported numerous attempts of repeat purchases by those potentially identified as individuals addicted to codeine.

In October 2022, the Commission on Human Medicines (CHM) considered the benefits and risks of codeine linctus, as well as the criteria for a prescription medicine included in 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;

The CHM recommended that the MHRA undertake a public consultation to obtain views on reclassification. The consultation ran from 18 July 2023 to 15 August 2023.

Conclusions of the review

Careful assessment of the benefits and risks and the significant number of responses to the consultation, has identified safety concerns associated with the supply of codeine linctus in the pharmacy setting. It has also found that there is limited evidence of effectiveness for codeine linctus in the treatment of short-term cough.

Following a review of all available evidence, including the responses to the public consultation, the CHM advised that codeine linctus is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction, or to be used for illegal purposes. Therefore, codeine linctus should be made a POM.

Alternative non-prescription medicines to treat short-term cough are available to the public and patients. Patients will still be able to access codeine linctus with a prescription from a qualified healthcare professional (HCP). This will ensure that the medicine is used safely and appropriately under medical supervision.

How the CHM reached their conclusions

The CHM examined a review of the benefits and risks of codeine linctus at two committee meetings (October 2022, and October 2023).

The MHRA gathered evidence on the benefits and risks of codeine linctus, from literature, Yellow Card reports, the Office for National Statistics (ONS), media and the National Poisons Information Service (NPIS).

Expert information was also obtained from a roundtable including HCPs and representatives from the General Pharmaceutical Council, trade associations, General Medical Council, Royal Pharmaceutical Society, National Crime Agency, the Scottish Government, Department of Health Northern Ireland, and the Department of Health and Social Care.

Additional evidence was provided from the public consultation to obtain wider opinions and personal experience.

Advice from the CHM

The CHM, the government's independent expert advisors on medicinal products, advised the following new risk minimisation measures for codeine linctus:

- Remove codeine linctus from pharmacy-only availability
- Restrict availability so that codeine linctus is only dispensed upon the presentation of a prescription
- Harmonise product and patient information to include safety warnings on addiction, in line with all prescription only opioid medicines
- Educational materials for HCPs.

Patients will still be able to access codeine linctus with a prescription from a qualified HCP. This will ensure that the medicine is used safely and appropriately under medical supervision.

Alternative non-prescription cough medicines are available for short-term cough. Patients are advised to speak to their pharmacist for advice.

Next steps

- The product information for all codeine linctus medicines will be updated to contain consistent information about addiction to opioids.

- The licences will be reclassified to POM status, enabling a patient to gain access once further medical diagnostic investigations have been undertaken as to the cause of their persistent cough.

- Further information is also available in the Drug Safety Update bulletin and press release, summarising the actions for HCPs and advice for patients, including signposts to support groups and self-help groups.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals (HCP) and the public of the latest updates.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

Consultation documents can be accessed from MHRA Public consultation on the proposal to make Codeine Linctus available as a prescription-only medicine (POM) - GOV.UK (www.gov.uk)

This report presents the MHRA's review of the benefits and risks of codeine linctus and the outcome of the responses to public consultation and expert advice on management of risks, as advised on by the CHM. Changes have been made to the ordering and wording used in the original assessment reports to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the review in October 2022 and October 2023. The MHRA and CHM will continue to monitor the safety of codeine linctus closely, however the information in this report will not be actively updated with new data or studies.

Background

Codeine, first discovered in the 1800s, is an opioid medicine which is metabolised into morphine and will produce analgesia (pain relief) and will also suppress coughing. Codeine linctus is available as a non-prescription medicine for supply under the supervision of a pharmacist (P) for the treatment of dry cough only.

In 2009, the CHM examined the availability of non-prescription codeine-containing medicines as the issue of addiction and dependence had not decreased since it was last reviewed in 2005 by the Committee on Safety of Medicines (CSM). It considered that regulatory actions were required to improve labelling and urge for responsible promotion of these products.

In 2019, following a review of dependence and addiction to opioid medicines, CHM recommended a number of improvements to product information for opioids used in the treatment of non-cancer pain, to provide consistent information for HCPs and patients. However codeine linctus available from the pharmacy is not authorised for the treatment of pain and therefore the patient information for codeine linctus was not updated. This means that information concerning addiction is not consistent with other codeine-containing medicines, although the risk remains.

At present there are 6 marketing authorisations (MAs) for codeine linctus, of which 5 are P products (7mg/5ml and 15mg/5ml) and 2 are prescription only medicines (POM) (25mg/5ml and one oral solution containing the combination of codeine 30mg and paracetamol 500mg/5ml). Non-prescription codeine linctus is marketed in pack sizes of 200ml and 2L.

Over the past 7 years there have been increasing reports that the combination of codeine linctus, promethazine and fizzy drinks is being used to make the recreational drink known as ‘Purple Drank’, ‘Lean’, ‘Dirty Sprite’ or ‘Sizzurp’ (herein collectively referred to as Purple Drank). This seems to be especially popular with young adults. 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. HCPs are also concerned of the risk of addiction associated with all forms of abuse and misuse of codeine linctus.

The MHRA undertook a review of the safety and efficacy (effectiveness) of codeine linctus, including the published literature and reports of dependence and diversion. We sought independent expert advice from the CHM to obtain their opinion on whether low strengths of codeine oral solution may safely be supplied without a prescription or should be upregulated to prescription only in line with the higher strength codeine solutions, to minimise the risk of misuse and subsequent addiction.

Human Medicines Regulations 2012 POM criteria

To be reclassified from P to POM a medicine must meet at least one of the criteria set out in the Human Medicines Regulations 2012, regulation 62(3):

- *It is likely to present a direct or indirect danger to human health, even when used correctly, if used without medical supervision; or*
- *It 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; or*
- *It contains substances or preparations of substances of which the activity requires, or the side effects require, further investigation; or*
- *is normally prescribed by a doctor for parenteral administration (that is, by injection).*

In addition, the licencing authority must take into account whether, if incorrectly used, the product is likely:

- to present a substantial risk of medicine abuse
- to lead to addiction, or
- to be used for illegal purposes.

Efficacy

Metabolism of codeine

Codeine is a prodrug, which is metabolised (broken down in the body) 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 (cough suppressant). Codeine is metabolised into morphine via CYP2D6, a polymorphic isoenzyme (has different forms) whose phenotype (characteristics) 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 into morphine-6-glucoronide via another enzyme, UDP-glucuronosyltransferase (UGT) 2B7.

Efficacy of codeine in cough

Codeine has been used as an antitussive (cough suppressant) for many years, although the evidence for efficacy is limited. Randomised controlled trials (RCT) have shown little efficacy in subacute cough but there is evidence of efficacy for morphine in the treatment of chronic cough.

Cochrane review of Over The Counter (OTC) medicines for cough 2014

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

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 RCTs to have efficacy, although only in about one third to half of all 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 and colleagues 2018

This review examined treatments in primary care for subacute cough. Acute cough lasts less than 3 weeks, subacute cough lasts 3 to 8 weeks and chronic over 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 RCTs patients 16 years of age and over 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. Overall, the authors highlighted the limited available evidence on therapeutic options for subacute cough, although showed that symptoms diminish over time in a self-limiting disease.

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 and colleagues 2007

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 enzyme 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 over 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 treatment. 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 (LCQ) 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 (forced expiry volume in 1

second) 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 to 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 LCQ score. 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 the end of the 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 of patients 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.

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 and therefore are likely to include 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 to 6% rapid metabolisers. Notably, 29% of African and Ethiopian population are ultra-rapid, therefore efficacy may differ according to ethnicity.

Safety

Codeine linctus had been previously reviewed by CHM in 2010, in relation to 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 U.S. Food and Drug Administration (FDA) issued a safety statement confirming a change to the label that codeine linctus should not be used in children under 18 years of age. The World Health Organisation (WHO) also 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”. As a consequence, there is variability between the product licences.

Opioid toxicity may manifest itself with symptoms similar to those associated with overdose, such as respiratory depression, pinpoint pupils, coma and death. Other side effects are constipation and associated disorders of the gut; dry mouth; psychiatric disorders such as euphoria, dysphoria (unhappiness), confusion; nervous system disorders such as dizziness, seizures, addiction, dependence, sleep disturbances; heart disorders; muscle rigidity; urinary retention, decreased libido, and skin or sensitivity disorders such as skin rashes, hives, itching and sweating.

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

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. 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.

Whilst this recreational use was initially identified in the US, Purple Drank is relatively easy to make with codeine linctus as it is available without a prescription. Hence this is a safety concern in the UK, and its use has been identified in schools and colleges reflecting use within the younger population. Promotion through social media can also lead people to believe there are fewer safety issues. Miuli (2020) highlighted epidemiological data which showed a heterogeneous diffusion of the misuse of this mixture, which is not exclusively linked to a specific type of user.

The website, Addiction resource, cites that a lethal oral dose of codeine is between 500mg to 1,000mg and the National Poisons Information Services for healthcare professionals highlight that a toxic dose is 2.5mg/kg. 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, although to date no UK deaths have specifically been linked to the abuse of Purple Drank. Fatal overdose from codeine is possible: data obtained from the Office for National Statistics, show from 2011 to 2021 codeine-related deaths registered in England and Wales increased from 88 to 200 although there is no information available about what formulation of codeine was involved in these fatal events other than they were not from compound formulations.

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 including codeine paediatric linctus, Lean (drug of abuse), Purple Drank (drug of abuse), Sizzurp (drug of abuse), Dirty sprite (drug of abuse) and Pholcodine linctus.	2	4	3	5	3	2
OTC branded (including Boots or 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.

Generally, Purple Drank is made at home using unmeasured amounts of codeine linctus and promethazine, however, it is also available ready-mixed to buy online, 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. Rosenberger and colleagues (2021) 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.

Yellow Card case reports

Three case reports involve the use of codeine oral solution. It should be noted that 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.

Case 1: 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 glorified in rap music, and there are online instructions on how to do this.

Case 2: 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.

Case 3: Stewart and McGlen (2019) 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 and paracetamol combination medicines and codeine and 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 online forums.

Diversion

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. Pharmacists experience is that codeine linctus is only requested by repeat users and some will only dispense against a prescription. Some people can be well-behaved and reasonable whilst others can be aggressive using intimidation and pressure to make a sale.

Over 18 months to August 2022, the MHRA have received approximately 3 referrals 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. In the pharmacy a 200ml bottle costs very little, however sells at greatly inflated prices online (£70 to £120), therefore reflecting demand and the lucrative business.

Most referrals coming to the MHRA have been for theft or diversion of the constituent products. As a result, enforcement of the issues is usually referred to the Police, with the General Pharmaceutical Council (GPhC) tackling the pharmacy overbuying aspect.

The MHRA Borderline unit considers the products when mixed have no medicinal use and thus is a substance of abuse. 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 or user, but also to the pharmacist and staff at wholesalers.

The Healthcare Distribution Association (HDA) have set tight controls on sales of codeine linctus, however not all wholesalers are members of the HDA, and larger amounts have been attempted than the cap will allow.

Drug interactions

The classes of medicines which have potential to interact with codeine are stated in the SmPC for codeine linctus. Corresponding detailed information is provided for the patient in the Patient Information Leaflet (PIL) and the label (outer carton) which advises the patient to speak to the pharmacist if they are taking any other medicines. Taking medicines that enhance the activity of CYP2D6 enzyme (such as rifampicin) at the same time as codeine can reduce blood levels of codeine, although raise blood levels of morphine, and increase the risk of potential side effects. Similarly, medicines that inhibit the activity of CYP2D6 enzyme will reduce metabolism to morphine but will not remove potential for side effects from codeine (for example cimetidine).

International Regulatory Activity

In 2016, the National Agency for the Safety of Medicines (ANSM) in France issued a warning note to pharmacists and doctors which urged them to make sure patients do not have a history of drug abuse and addiction before prescribing codeine containing cough syrup. Since July 2017, following a review of opioid use in France, ANSM took further actions to change access to all codeine-containing medicines to prescription only (end of access to self-medication for analgesic medicinal products containing codeine - OFMA) and all oral

formulations of promethazine have required a prescription since Jan 2020 (Order of 21 January 2020 on the classification of poisonous substances on the lists - Légifrance (legifrance.gouv.fr)).

In 2018, a television news item (How to halt a cough-syrup addiction) highlighted that 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.

In February 2018, the Therapeutic Drugs Administration in Australia also took regulatory action to change access to all codeine medicines to prescription only to reduce the rate of codeine-related deaths.

Indirect dangers

The potential for indirect danger occurring from non-prescription use of a medicine arises mainly from the use of the medicine without medical supervision in groups of patients for whom it is not suitable. In these circumstances, danger can arise from mistaken diagnosis, or exclusions that are deliberately or inadvertently not heeded.

The following potential indirect dangers have been identified for pharmacy supply of codeine linctus:

Intentional misuse – risk of non-prescription 'off-label' use (use outside the terms of the marketing authorisation)

- It is possible that some excluded categories of people with persistent cough may try to purchase codeine linctus in the pharmacy.

Indirect Danger resulting from missed underlying risk factors and medical conditions

The symptoms of dry cough are considered suitable for self-assessment by patients, supplemented by advice from a pharmacist, although if symptoms of cough exist alongside additional breathing symptoms, the possibility of other underlying conditions being present is greater. Groups of patients who may experience serious risk associated with opioid medicines, including codeine linctus are:

- Patients suspected of drug abuse.
- Patients with kidney or liver disease; as codeine may accumulate.
- Patient with asthma or bronchitis.
- In children below the age of 12 years; due to an increased risk of developing serious and life-threatening adverse reactions.

- In women during breastfeeding (as codeine and morphine may be present in breast milk).
- In a rare group of patients who can digest codeine very quickly into morphine.

Duration of treatment

It is possible in certain situations that a patient may suffer a worsened outcome as a result of unsupervised use of non-prescription codeine if they continue to use codeine linctus in circumstances where alternative treatments might have been more suitable.

The maximum duration of treatment with codeine linctus has not been set. If a patient continues to take codeine linctus for prolonged periods of time, then they have the potential to become tolerant to the beneficial effects and feel they need more to gain the same effect. Guidance is provided to patients taking codeine tablets, that if symptoms do not improve after 3 days, then they should seek the advice of a doctor.

An acute dry cough (lasting less than 3 weeks) and a subacute cough (lasting between 3 to 8 weeks) would generally resolve itself. However, if cough becomes persistent then the patient should be seeking care from a physician to manage their symptoms, who would be able to prescribe codeine linctus if it was considered beneficial for the patient.

CHM consideration of benefit : risk, October 2022

In October 2022, upon consideration of the benefits and risks, the CHM considered that codeine linctus met the 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;

The CHM also considered that it should go to public consultation to gain wider views.

Summary of Responses to Public Consultation

This is a summary of the responses to the public consultation on the MHRA proposal to reclassify codeine linctus from P to POM.

All responses have been fully considered, however owing to the large number of responses, individual responses will not be published. Some example comments are provided, and confidentiality maintained.

A total of 992 responses were received, of which 868 completed all questions in the consultation.

A total of 587 (59%) of the 992 responses agreed that codeine linctus should be reclassified to prescription only medicine. Of those who completed the whole survey, 522 (60%) of the total 868 were in favour of reclassification.

A total of 358 (36%) of the 992 responses were against. Of those who completed the whole survey, 322 (37%) of the total 868 were against reclassification.

A total of 47 (5%) of the 992 responses were unsure. Of those who completed the survey, 24 (3%) were not sure.

An overall summary of the responses to each question is presented in Annex I of the consultation response.

The majority of responses were received from persons aged between 31 to 45 years of age.

Of all 992 responses, most (573 responses, 65%) came from HCPs and 220 (25%) came from members of the public. Six (1%) responses came from a patient representative organisation, 31 (4%) came from trade or professional associations or organisations and 39 (4%) had personal experience of the effects of codeine linctus. Ten (1%) responses came from other sources.

Of those 587 respondents that agreed with the proposal to reclassify to POM, 419 (78%) were current and retired HCPs, 64 (12%) came from a member of the public, 27 (5%) were representatives of trade or professional association or an organisation, 4 (1%) were representatives of patients, and 18 (3%) had personal experience, either as an individual or from family connections. Other responses came from police drug liaison officers and a safer community network (with members from the emergency services and local authorities). Fifty-Four (9%) did not say who they were.

Of those that disagreed, 140 (43%) were current or retired HCPs, 151 (47%) were members of the public, 4 (1%) were representatives of patients, 4 (1%) were representatives of trade or professional association or organisation and 25 (8%) had personal experience either as an individual or from family connections. Of the total who disagreed with the proposal, 32 (9%) did not say whether they were a HCP, representative of any sort or have personal experience.

Of those that were unsure, a total of 47 responses were received and the majority did not complete all parts of the consultation. Twenty-nine respondents revealed their affiliation, which included: 5 (21%) members of the public, 2 (8%) patient representatives including a social worker in third sector support services, 18 (75%) HCPs including a member of the public with personal and healthcare experience, 3 (13%) representatives of trade or professional associations or an organisation and one (4%) with personal and healthcare experience.

More information on the responses is available in our Consultation Response.

Discussion

Codeine linctus is authorised as an antitussive in the treatment of a dry unproductive cough. Codeine is an opioid and therefore there is a risk of addiction. Codeine is also a prodrug which is metabolised to morphine via the polymorphic enzyme, CYP2D6. Consequentially its efficacy is variable as it is dependent on the individual's enzyme active status which can vary with their genetic makeup. Therefore, those individuals who are able to metabolise codeine more efficiently to gain the beneficial effects, may also experience increased side effects such as euphoria. There is little clinical evidence to support efficacy as an antitussive in the treatment of acute or subacute cough, although there is some evidence that the metabolite, morphine, may be effective in the treatment of chronic cough. As a non-prescription medicine, there is the potential that patients with chronic cough do not seek medical help and rely on codeine linctus with the risk of dependence and addiction with continual use. Similarly, the patient's underlying medical condition may need to be fully investigated to explore the potential cause of the chronic cough and suitable treatment. Alternative non-prescription medicines are available for the treatment of short-term dry cough.

Codeine has also been identified as an ingredient of the recreational drink known as 'Purple Drank'. In August 2022, the MHRA were also approached by a number of stakeholders who highlighted that they were either subjected to aggressive behaviour by persistent purchasers or were aware of criminal activity in order to obtain the linctus followed by sales on illegal websites.

In October 2022, CHM recommended that codeine linctus met the second prescription only criterion as defined under the Human Medicine 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"*

and that it should go to public consultation.

A large number of responses (992) were received to the public consultation on the proposal to reclassify codeine linctus to POM which included 4 responses from police drug liaison officers of 4 different constabularies, and a representative of pharmaceutical wholesalers, who commented that codeine linctus was associated with illegal activities. It was also generally recognised that individuals could become addicted to codeine. Therefore, this supported the regulation 62(3) under subsection (c) that a decision should consider whether the medicine is:

> *(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;

The majority of responses were in favour of the proposal to reclassify codeine linctus to POM. Whilst there were comments against in terms of access to primary care, sufficiency of current systems in place and insufficient barriers to addiction, there was also agreement that it would provide a barrier to recreational use. An important point was made that recreational use differed from addiction, however there is the potential risk that individuals can become unintentionally addicted, whether codeine was taken recreationally or following an initial prescription. This potential risk is dependent upon the dose and duration of treatment and the susceptibility of the patient to develop opioid dependence or addiction.

For some who agreed on the proposal, there was also an agreement that it would have an impact on primary care, although this was considered to be minor and would be short-lived. In contrast, others who agreed with the proposal, also raised a considerable concern in terms of treating cough over the winter months and the impact on care. However, those in opposition to the proposal highlighted that there were alternatives which were not addictive, and both pharmacists and independent prescribers are able to advise on appropriate treatment. Access to GPs is an issue, although this is a more general concern for which action is being undertaken at local levels. Comments also raised the issue of social and geographical demographics, indicating areas where there would be greater impact such as those with fewer GP services compared with numbers of pharmacies. However, views also suggested that all patients would be treated equally, but also that the genuine use of codeine linctus was limited overall.

Some respondents highlighted the potential risk that individuals addicted to codeine, would simply move to obtain codeine from alternative sources such as online unregulated sites, or switch to OTC codeine combination medicines such as codeine with paracetamol or codeine with ibuprofen which produce significant adverse drug reactions if taken in excess. In these cases, close monitoring by a HCP was considered important. However, the benefits achieved by reclassifying to POM were considered to outweigh the risks.

Some unsolicited responses called for the reclassification of all codeine medicines, although this was not supported by others.

It was clear that there was a desire for education for HCPs (including front line staff), patients and the public. This was evident in many responses and in proposals to minimise further risk, including:

- improve the product information,

- provide educational materials for HCPs and patients / carers

The provision of educational materials was proposed to be in a variety of formats including booklets, posters or electronically and supported by an awareness campaign which does not create patient stigma. The development of the diverse array of material would require input from patients and professional organisations to ensure that a correct balance could be ensured. Although training on how to deal with aggressive individuals may already be available by professional organisations (for example Managing Conflict at Work (rpharms.com)). Additional help is available through support sites such as FRANK. The MHRA also published a patient leaflet on the potential risk of addiction to opioid medicines (opioid medicines and the risk of addiction (publishing.service.gov.uk))

Expert advice

The CHM, the government's independent expert advisors on medicinal products, commented on the lack of clinical evidence of codeine efficacy in acute or subacute cough, although noted sufficient evidence for its metabolite, morphine, in the treatment of chronic cough. However, CHM was conscious of the following points as highlighted in the overall review and responses from public consultation:

- the lack of effectiveness in the treatment of short-term cough
- the addictive nature of codeine and previous warnings that had been added to product information, and yet codeine linctus is now being used as a primary ingredient in the product of recreational drink, commonly named "Purple drank", increasingly popularised through social media, making it appealing to young adults
- regulatory actions have already been taken in France, Nigeria and Ghana as young adults were becoming addicted to codeine oral solutions
- the MHRA have been receiving an increasing number of reports of diversion, including over-ordering and thefts from warehouses, indicating an increase in the uptake of codeine linctus for recreational use
- codeine can be toxic at a dose of 2.5mg/kg and potentially fatal between 500mg to 1,000mg depending on whether the individual is opioid naïve or used to the effects
- the high number of responses to the public consultation (ARM103) and the overall support for the proposal to reclassify codeine linctus to POM
- codeine linctus is likely only to be prescribed in patients with chronic cough who are already receiving primary care
- the general misuse of codeine linctus is a growing concern, particularly with the availability of the large bottle sizes
- the potential risk that patients may switch to codeine combination products currently available without prescription, although the emerging evidence from Australia indicates a decrease in the number of serious adverse reactions associated with the overuse of codeine medicines following action taken in 2018 to reclassify all codeine products to POM and was considered a positive outcome for patient safety
- the availability of other non-prescription medicines for the treatment of short-term cough

In the light of evidence derived from the consultation and that codeine linctus is being incorrectly used, can lead to addiction and is used for illegal purposes as defined in paragraph 4 of the Human Medicine Regulations 2012, the Commission advised that codeine linctus met the second prescription only criterion under paragraph 3 (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. Therefore, the availability of codeine linctus should be changed from a pharmacy medicine (P) to a prescription only medicine (POM).

The Commission also advised that product information should be harmonised with prescription opioid medicines to include safety warnings on addiction for patients and HCPs as endorsed by CHM December 2019.

Conclusion

Careful assessment of the significant number of responses to consultation on the reclassification of codeine linctus for treatment of dry unproductive cough in adults and children aged over 12 of age without difficulties in breathing, has identified safety concerns associated with the supply of such a product in the pharmacy setting.

Following consideration of the lack of evidence for effectiveness for acute cough, the likelihood of dependence if used for long periods of time, and the potential delay of individuals in seeking advice from their HCP, and all available evidence, including the responses to the public consultation, the CHM advised that codeine linctus is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction, or to be used for illegal purposes. Therefore, the POM criteria, in particular criterion 2 (there is frequently incorrect use which could lead to direct or indirect danger to human health) applies to codeine linctus.

Patients will still be able to access codeine linctus with a prescription from a qualified HCP. This will ensure that the medicine is used safely and appropriately under medical supervision.

Alternative non-prescription cough medicines are available for short-term cough. Patients are advised to speak to their pharmacist for advice.

Next steps

- The product information for all codeine linctus medicines will be updated to contain consistent information about addiction to opioids.
- The licences will be reclassified to POM status, enabling a patient to gain access once further medical diagnostic investigations have been undertaken as to the cause of their persistent cough.
- Further information is also available in the Drug Safety Update and press release, summarising the actions for HCPs and advice for patients, including signposts to support groups and self-help groups.

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Glossary of terms

Include a glossary of terms used in alphabetical order. Consult past safety PARs for examples and to use consistent definitions. If consulting externally, consider seeking advice on whether the glossary is complete or whether any other terms need to be defined.

For example:

Advanced Nurse Practitioner
Advanced Nurse Practitioner means a nurse with Level 7 MSc qualifications in clinical assessment, which includes history taking, physical examination and independent prescribing.

Adverse drug reaction
A suspected side effect of a medicine.

Analgesia
Pain relief.

Analgesic
A medicine which will provide pain relief.

Antitussive
A cough suppressant used to achieve temporary relief from coughing, although will not stop coughing altogether.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Efficacy
The effectiveness of a medicine.

Epidemiology
The scientific study of diseases and disorders and how they are found, spread, distribution, and controlled in groups of people

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Metabolise
To digest or breakdown a substance in the body

Non-pharmacological
A treatment which does not involve a medicine**.**

Patient Information Leaflet

Medicine packs includes a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Phenotype
The physical characteristics of something living, especially those characteristics that can be seen. A person's phenotype is determined by both their genetics (inherited family traits) and environmental factors.

Polymorphic enzyme
An enzyme which presents in different forms, changing its activity.

Randomised controlled trial
A study or experiment to examine the effectiveness of a substance or treatment.

Spirometry
A lung function test.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at:
https://www.gov.uk/guidance/find-product-information-about-medicines