MHRA PUBLIC ASSESSMENT REPORT

Codeine and dihydrocodeine-containing medicines: minimising the risk of addiction

September 2009

EXECUTIVE SUMMARY

(Please note that this summary is intended to be accessible to all members of the public, including health professionals)

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports we discuss evidence-based assessments of safety issues for a particular drug or drug class, and changes made to the product information on the basis of this evidence which will help safeguard public health. The following MHRA Public Assessment Report discusses new measures which will be put into practice to minimise the risk of addiction to medicines containing codeine or dihydrocodeine (DHC).

Codeine and DHC are analgesics (pain relievers) and cough suppressants, and are contained in many medicines sold over-the-counter (OTC) in UK pharmacies. In these medicines, codeine or DHC is usually combined with other pain-relievers such as paracetamol or ibuprofen and sometimes with other substances as well. Taken in the correct manner and for the right purposes, codeine and DHC are very effective and acceptably safe medicines. There is a risk, however, that people taking codeine or DHC-containing medicines may deliberately, or inadvertently, overuse or become addicted to these products. Because of this risk, the predecessor to the Commission on Human Medicines (CHM; an independent body which gives advice to government Ministers about the safety, quality, and efficacy of medicines) issued the following advice in February, 2005 in relation to OTC medicines containing codeine or DHC in solid dose forms:

- Strengthen the warnings on the SPC[a], PIL[b] and label to reflect the importance of not taking the medicines for more than three days continuously without medical review, and to warn about the risks of addiction and headache from overuse[c]
- Limit the pack size to 32 tablets by voluntary agreements with companies, with any pack sizes available above 32 tablets labelled as 'dispensing only'
- Agree, with companies, a responsible approach to promotional activities

The product information was updated according to these recommendations, and can be found in the PIL accompanying the medicine and on the Electronic Medicines Compendium (product information) website.

In January 2009, the All-Party Parliamentary Drug Misuse Group (APPDMG; a group of members of parliament who meet to discuss issues and concerns on drug misuse) published a report[1] on physical dependence and addiction to prescription and OTC medicines. The report presented evidence received from the Royal Pharmaceutical Society of Great Britain, the self-help group Over-Count and the MHRA, and made a number of recommendations[d] to further reduce the risk of misuse of medicines; in particular, OTC medicines containing codeine or DHC.

Conclusions

[a] Summary of Product Characteristics: product information
[b] Patient Information Leaflet: product information for patients
[c] A constant headache caused by the overuse of OTC painkillers
[d] Some APPDMG recommendations were outside of the MHRA's responsibilities

On the basis of the information from the APPDMG report, new sales data and new information from Self Help groups the CHM further considered the issue of the risk of overuse and addiction to OTC medicines containing codeine or DHC in solid dose forms, and recommended the following measures:

Indications
All indications[a] relating to colds, influenza, coughs and sore throats, and references to minor painful conditions in product information will be removed. The remaining list of indications will be for the short-term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

Patient Information Leaflets (PIL) and labels
The PIL and medicine labels will state that the products are for short-term use only, for the treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen and aspirin alone, and that the products can cause addiction or overuse headache if used continuously for more than three days. In particular, the following warning will appear clearly and prominently on the front of the pack:

'Can cause addiction. For three days use only'

The PIL will also carry information about the warning signs of addiction, ie, if the medicine is needed for longer periods and in higher doses than recommended, and if stopping the medicine makes you feel unwell but you feel better when you start taking it again.

Pack size
All pack sizes greater than 32 tablets of solid dose codeine or DHC-containing OTC medicines, including effervescent[b] formulations, will no longer be available as pharmacy[c] products (ie, they will only be available on prescription).

Advertising
Advertisements will be updated to reflect the new indications and warnings, and will not contain references to painkilling power and strength. Also, all advertisements will include the following statement:

'Can cause addiction. For three days use only'.

The MHRA are currently implementing these measures, and all products with the updated information will be available on pharmacy shelves during 2010. As with all medicines, the MHRA will continue to closely monitor the safety of all codeine and DHC-containing products.

[a] Conditions or diseases that the medicine is licensed to treat
[b] Soluble
[c] Pharmacy products are sold OTC

1. INTRODUCTION

(See glossary for explanation of terms)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports we discuss evidence-based assessments of safety issues with a particular drug or drug class, and changes made to the product information on the basis of this evidence which will help safeguard public health. The following MHRA Public Assessment Report discusses new measures which will be put into practice to minimise the risk of addiction to medicines containing codeine and dihydrocodeine (DHC) in solid dose form.

2. BACKGROUND

Codeine and DHC are opiate analgesics and cough suppressants, and are contained in many medicines sold over-the-counter (OTC) in UK pharmacies. In these medicines, codeine or DHC is usually combined with other pain-relievers such as paracetamol or ibuprofen.

Under the Misuse of Drugs Act and the Prescription Only Medicines (Human Use) Order 1997, there are provisions for small quantities of these controlled drugs to be included in non-prescription medicines and sold through pharmacies only. They may include doses of up to 25·6 mg codeine phosphate (ie, 12·8 mg per tablet for a two- tablet dose) and up to 14·92 mg DHC tartrate (ie, 7·46 mg per tablet for a two- tablet dose).

There are 42 authorised products available from pharmacies that contain codeine, and four which contain DHC. In these products, codeine or DHC are combined with other active ingredients, for use as painkillers. Of the codeine-containing products, 36 are combined with paracetamol, two with ibuprofen and four with aspirin. The DHC-containing products are all combined with paracetamol. Some codeine-containing products also include other active ingredients, such as caffeine.

Examples of a range of commonly used codeine and DHC containing products are included in the table at **annex 1.**

There is a risk that people taking codeine or DHC-containing medicines may deliberately, or inadvertently, overuse or become addicted to these products. Because of this risk, the predecessor to the Commission on Human Medicines (CHM; an independent body of experts who give advice to government Ministers about the safety, quality, and efficacy of medicines) issued the following advice in February, 2005:

- Strengthen the warnings on the SPC[a], PIL[b] and label to reflect the importance of not taking the medicines for more than three days continuously without medical review, and to warn about the risks of addiction and headache from overuse
- Limit the pack size to 32 tablets by voluntary agreements with companies, with any pack sizes available above 32 tablets labelled as ‘dispensing only’
- Agree, with companies, a responsible approach to promotional activities

[a] Summary of Product Characteristics: product information
[b] Patient Information Leaflet: product information for patients

The product information was updated according to these recommendations, and can be found in the PIL accompanying the medicine and on the Electronic Medicines Compendium (product information) website.

However, despite these actions, concerns about addiction to OTC medicines containing codeine or DHC continued to appear in the media. In the 2007–2008 parliamentary session, the All-Party Parliamentary Drug Misuse Group (APPDMG) carried out an inquiry[1] into physical dependence and addiction to prescription and OTC medicines. (An All Party Parliamentary Group is cross-party and includes members of both houses of parliament who meet, relatively informally, to discuss a particular issue of concern). The inquiry considered evidence received from the healthcare, pharmaceutical and drug treatment sectors, as well as from support groups and individuals with experience of misuse and addiction.

The Royal Pharmaceutical Society of Great Britain (RPSGB) made a submission to the APPDMG inquiry, that outlined how they address the issue of misuse of Prescription Only (POM) and OTC medicines through their regulatory and professional roles. RPSGB inspectors help to monitor local trends in drug misuse and advise pharmacists on appropriate action when misuse is suspected. The RPSGB highlighted a recent study[2] that showed that pharmacists are confident in their ability to identify customers whom they suspect to be misusing OTC medicines and that they employ various strategies to limit access to medicines that might be misused. However, the study also revealed that some pharmacists lack confidence in raising concerns with the customer.

In the report[1] of the APPDMG inquiry, published in January 2009, a number of recommendations[a] were made, based on the evidence received, to reduce the risk of misuse of medicines, in particular, OTC medicines containing codeine or DHC.

[a] Some APPDMG recommendations were attributed to the MHRA but fall outside the Agency's remit

3. EVIDENCE OF ADDICTION AND MISUSE

There is no evidence to suggest that addiction to, or misuse of, OTC medicines containing codeine or DHC is increasing. Indeed, the APPDMG report recommends that more research should be undertaken in the field of dependence to prescription and OTC medicines, to determine the scale and related implications of the problem.

The self-help group Over-Count[a] reported that it had helped 16 000 people between 1993 – 2007 who had approached them with a problem about dependency to an OTC product (see APPDMG report). Concerns about addiction to OTC products containing codeine or DHC also continue to appear in the media.

4. RISK MINIMISATION TOOLS

After consideration of the available evidence, the CHM was asked to consider the following measures to minimise the risk of addiction to OTC medicines containing codeine or DHC.

5.1 Reduce the pack size

Alongside strengthened labeling/PIL warnings, the MHRA had already taken the following action to reduce the pack size of OTC medicines liable to abuse or misuse:

Codeine –In July 2005, a voluntary agreement was reached with manufacturers to restrict pack sizes of OTC medicines containing codeine or DHC to 32 tablets. These voluntary measures have been implemented.

Pseudoephedrine and ephedrine – In response to reports about the illicit manufacture of methylamphetamine using OTC medicines containing pseudoephedrine (PSE) or ephedrine (EPH), the CHM recommended a reduction in pack size of OTC medicines containing PSE and EPH and to limit the number of packs that can be sold per transaction to one. Sales figures for one brand of a PSE-containing product and its generic equivalent of PSE tablets sold by a major pharmacy chain show a 26% drop in the number of tablets sold between July 2008 – August 2009.

Paracetamol – In response to concerns about the number of deaths from paracetamol poisoning. measures were introduced in 1998 to limit the pack sizes of paracetamol tablets and capsules to 16 for General Sales List (GSL)products[b], and 32 for Pharmacy Only[c] products, with a provision for pharmacists to supply up to 100 tablets or capsules in such packs without prescription if they think it appropriate.

Aspirin – Legislative restrictions similar to those imposed on paracetamol were made for aspirin, with some exemption for low-strength 75 mg products.

Ibuprofen and other OTC non-steroidal anti-inflammatory drugs – Voluntary and licensing restrictions were agreed with industry to ensure consistency of OTC analgesics.

[a] A charity and online support group for the issue of OTC addiction and misuse
[b] Can be sold from a wide range of shops
[c] Can only be sold from a pharmacy

In relation to the current concerns about misuse of codeine-containing OTC medicines,the CHM considered a number of options regarding changes to their pack size:

Option 1 – Do not impose any further restrictions on the pack size.

There was little new evidence of an increase in addiction to, or misuse of, OTC medicines containing codeine or DHC. Pack sizes were reduced in 2005 so it could be argued that no further pack size reduction was needed.

However, the APPDMG report recommended that the MHRA should reduce the pack size of codeine-containing painkillers to 18 tablets, and make them only available after consultation with a pharmacist.

Option 2 – Restrict the pack size of OTC medicines containing codeine or DHC to 3 days supply (i.e. 18 tablets for ibuprofen-containing products and 24 tablets for paracetamol-containing products).

5.2 Address the anomaly with effervescent co-codamol

When the voluntary pack size limit of 32 for codeine or DHC-containing tablets was implemented in 2005, generic packs containing more than 32 and up to 100 co-codamol[a] effervescent tablets were relabelled as dispensing packs but they continued to be sold over the counter in pharmacies; this form is not covered by the paracetamol pack size restrictions which only apply to solid dose forms. The CHM considered the options for all codeine and DHC-containing OTC medicines, including effervescent formulations.

5.3 Improve patient information and support

Although CHM had already taken action in this regard, they considered further improvements, including making the warning about risk of addiction more prominent on the pack – for example, by placing it on the front separate from the rest of the patient information.

CHM were helped in their task of improving patient support by members of the Expert Advisory Group (EAG) on Patient Information who looked at the existing warnings and considered the need for a more prominently-positioned warning on the label of OTC codeine and DHC medicines about the risk of addiction.

5.4 Review advertising and promotion guidelines

The CHM also advised on the advertising and promotion of codeine or DHC-containing OTC medicines. They considered a number of options:

Option 1 – maintain the current position.

There is no clear evidence to link advertising with addiction or misuse.

[a] Combined painkiller containing codeine and paracetamol

However, encouragement to try the products through advertising may result in users of single-ingredient painkillers switching to products containing codeine or DHC which carry a risk of addiction if overused.

Option 2 – Recommend a ban on all advertising of OTC medicines containing codeine or DHC.

This was a recommendation of the APPDMG. However, it was not supported by the self-help groups.

Option 3 –Recommend further conditions on the advertising of OTC medicines containing codeine or DHC including adding a warning that the products contain these ingredients, and that long-term use can lead to addiction. This warning would be supported by an industry-agreed Code of Practice.

A clear warning in advertising of the potential harmful effects of misuse of codeine or DHC-containing OTC medicines would help raise awareness of the risks. It would also ensure that people who wish to use these medicines have information at the outset about the dangers of addiction, which is consistent with warnings on the labels and PILs.

5. CONCLUSIONS

On the basis of current evidence, the CHM recommended the following measures to minimise the risk of overuse and addiction to OTC medicines containing codeine or DHC:

LABELS

The labels will state:

Front of Pack

- Can cause addiction
- For three days use only

These requirements are in addition to the normal statutory provisions and should be prominently displayed.

This information will also be included in section 4.4 of the SPC under the heading “The label will state”.

Back of Pack

- List of indications as agreed in 4.1 of the SPC
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

These requirements are in addition to the normal statutory provisions and should be prominently displayed.

This information will also be included in section 4.4 of the SPC under the heading “The label will state”.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Indications (section 4.1)

All indications in the SPC relating to colds, influenza, coughs and sore throats, and references to minor painful conditions will be removed. The remaining list of indications will be for the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

PATIENT INFORMATION LEAFLETS (PIL)

The PIL will state:

Headlines section (to be prominently displayed)

- This medicine can only be used for …….(indications)
- You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days it can make them worse.

Section 1: What the medicine is for

- Succinct description of the indications from section 4.1 of the SPC

Section 2: Before taking

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take a painkiller for headaches for more than three days it can make them worse.

Section 3: Dosage

- Do not take for more than 3 days. If you need to use this medicine for more than three days you must speak to your doctor or pharmacist.
- This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

Section 4: Side effects

- Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional. Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0808 100 3352 (available between 10am–2pm Monday – Friday) or fill in a paper form available from your local pharmacy.

New section: How do I know if I am addicted?

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time
- You need to take more than the recommended dose
- When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again.

These requirements are in addition to the normal statutory provisions and should be prominently displayed.

This information will also be included in section 4.4 of the SPC under the heading “The leaflet will state”.

PACK SIZE

All packs greater than 32 of codeine or DHC containing OTC medicines in solid dose form, including effervescent formulations, will no longer be available as P products (ie, they will become prescription-only).

ADVERTISING
The advertising and promotion code of practice will be updated to reflect the new indications and warnings, and all advertisements will carry the statement:

‘Can cause addiction. For three days use only’.

The MHRA is in the process of implementing these measures, and all products with the updated information will be available on pharmacy shelves during 2010. As with all medicines, the Agency will continue to closely monitor the safety of all codeine and DHC-containing products.

6. REFERENCES

1. All-Party Parliamentary drugs Misuse Group Inquiry into physical dependence and addiction to prescription and over-the-counter medication. http://www.codeinefree.me.uk/img/APPDMGPOMOTCRptFinal.pdf (accessed September 2009)

2. Mackridge A, McKenny C. Abuse of over the counter medicines: the pharmacists' perspective. *IJPP* 2007;**15**(Suppl. 2):B70.

7. GLOSSARY

Addiction
Developing a **dependency** on a drug and having withdrawal symptoms if you stop taking it

Analgesic
Pain-reliever

Aspirin
Type of pain relief medicine

Brand leader products
The brand of a particular product that most people choose to buy

Caffeine
A drug that increases wakefulness and mental activity

Codeine
Type of pain-relief medicine, also used to treat cough

Dependency
Continuing to take a drug even though there are adverse consequences

Dihydrocodeine
Type of pain relief medicine

Dispensing
Selling drugs or medicines, as directed by a prescription

Effervescent
Soluble drug

Ephedrine
A drug that narrows blood vessels and widens airways, used mainly to clear a blocked nose (a nasal decongestant)

Generic
The chemical or ‘scientific’ name of a drug (not the brand name)

Ibuprofen
Type of pain-relief medicine

Methylamphetamine
A Class A controlled drug that is illegal to possess, supply or manufacture. It causes feelings of exhilaration

Non-steroidal anti-inflammatory drugs
Type of pain-relief medicine

Opiate
A pain-relief drug derived from opium (a substance found in opium poppies)

Overuse headache

A constant headache caused by the overuse of OTC painkillers

Paracetamol
Type of pain-relief medicine

Pseudoephedrine
A drug that narrows blood vessels, used mainly to clear a blocked nose (a nasal decongestant)

Statutory
Required or authorised by law

Withdrawal
Symptoms such as sweating or vomiting, caused by not taking (or withdrawing from) a drug that one has become **addicted** to.

8. ANNEX 1: Table of commonly-used authorised over-the-counter products containing codeine/dihydrocodeine

PRODUCT NAME	INGREDIENTS	STRENGTH	PACK SIZES*
Co-codamol tablets	Codeine phosphate Paracetamol	8 mg 500 mg	20, 21, 25, 28, 30, 32
Co-codamol effervescent tablets	Codeine phosphate Paracetamol	8 mg 500 mg	7, 10, 14, 20 28, 30, 32, 56, 60, 84, 90, 100
Solpadeine Max (tablets or soluble tablets)	Codeine phosphate Paracetamol	12·8 mg 500 mg	Tablets: 6, 10, 12, 16, 20, 24, 30, 32 Soluble tablets: 8, 16, 20
Solpadeine Plus (Tablets or soluble tablets)	Codeine phosphate Paracetamol Caffeine	8 mg 200 mg 30 mg	Tablets: 4, 6, 12, 16, 24, 32 Soluble tablets: 4, 8, 12, 16, 24, 32
Nurofen Plus tablets	Codeine phosphate Ibuprofen	12·8 mg 200 mg	6, 8, 12, 16, 18, 24, 32
Syndol tablets	Codeine phosphate Paracetamol Caffeine Doxylamine suucinate	10 mg 450 mg 30 mg 5 mg	4, 10, 20, 30

Paramol (tablets or soluble tablets)	Dihydrocodeine tartrate Paracetamol	7·46 mg 500 mg	12, 24
Codis 500 soluble tablets (effervescent)	Codeine phosphate Aspirin	8 mg 500 mg	6, 8, 12, 16, 24, 32

*Not all pack sizes may be marketed