Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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Recent observational studies have suggested a possible association between insulin glargine and an increased risk of cancer. In this issue, we summarise the latest data. The results are not entirely consistent, and can neither confirm nor exclude a relationship between insulin glargine and cancer. Therefore, the European Medicines Agency has advised that no change in recommendations for use is required at present—see p 3 for further information.

In July 2009, the Commission on Human Medicines considered an update on the impact of the measures implemented to contain potential misuse of nasal decongestants that contain pseudoephedrine and ephedrine in the illicit manufacture of the Class A drug methylamphetamine (crystal meth). CHM advised that these medicines may continue to be sold as pharmacy medicines, provided the measures continue to be effective. A reminder of these measures is on p 5.

CHM has also recently advised on a package of measures to minimise the risk of overuse and addiction to over-the-counter medicines containing codeine or dihydrocodeine. The package of measures includes changes to indications, labels and leaflets, pack size, and advertising. See p 6 for further information.

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The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

Yellow Card scheme update

How to complete an online Yellow Card

You can complete a Yellow Card to tell us about a suspected adverse drug reaction to any medicine (including herbal products, over-the-counter medicines, and unlicensed medicines) or vaccine. Report online at www.yellowcard.gov.uk. Alternatively paper Yellow Cards can be found in the back of the British National Formulary or obtained by contacting the MHRA on 0800 731 6789.

This is an example of a completed electronic Yellow Card and shows the key information which should be completed. It should only take around 15 minutes, but please don't be put off from reporting if you don't have all the information.

1.

Please provide details of the suspected adverse drug reaction. Information on dates and outcome help in the assessment of the Yellow Card.

2.

The name of one or more suspect drug(s) or vaccine(s) thought to have caused the adverse drug reaction is required. If possible please provide the drug brand name(s).

4.

The batch number is key in detecting potential batch defects.

6.

Information given in this section is often useful to help assess whether other factors may have caused, or contributed to, the adverse reaction. A case may be followed up with you to request additional relevant information if available, so if none is available please indicate this.

7.

At least one of the following is required:

- age
- sex
- weight
- initials
- height
- or a local identification number.

A local patient reference number has been provided. This may be the patient practice reference number, or a reference which helps you know who the Yellow Card refers to. It means the patient can be identified if we contact you for additional information.

YellowCard
Helping make medicines safer

MHRA

Thank you very much for completing a Yellow Card report on the suspected side-effect of a medicine. We really appreciate your contribution
because evey Yellow Card we receive helps us to monitor the safety of medicines. Below is a copy of your Yellow Card report which has been entered into our database.

If you have any more information about the suspected side effect, or if there are any changes to the details you provided on the Yellow Card report, please let us know, quoting the **Yellow Card Registration Number: GB-MHRA-EYC 9999999**

Suspect Reaction

Suspect Reactions Added	Outcome of the Reaction	Start Date	End Date
Anaphylactoid reaction, swelling face	Recovered	10 October 2008	12 October 2008

Do you consider the reaction to be serious? Yes. Life threatening

3.

Please provide an assessment of the seriousness of the reaction(s); here, reactions were life threatening.

Description of the suspect reaction (including the sequence of events, any treatment, etc)

After 4 hours patient developed swollen face, severe itching, and difficulty breathing. Treated with adrenaline. Sibutramine stopped

Suspect Drug

Name of the suspect drugs(s) you suspect caused these suspected reaction(s)

Medicine	Start Date	End Date	Dosage Indication	Action taken for reaction	Batch No.	Route of Administration
Sibutramine	10 October 2008	11 October 2008	10mg	Drug withdrawn	X12345	Oral

Did the patient take any other medication in the last 3 months (including prescription, over the counter or herbal medicines)? No

Other Medication Taken in the last 3 months

Other information you think might be important, including any other medical condition or allergies that the person might have

Penicillin allergy

5.

You can tell us about other drugs that have been taken in the last 3 months. This information helps us in our evaluation of whether the reaction was caused by the suspect drug.

YellowCard
Helping make medicines safer

MHRA

Yellow Card Registration Number: GB-MHRA-EYC 9999999

Patient Details

Initials	GT	Weight (kg)	
Gender	Female	Height (m)	
Age at time of reaction	13 Years, 0 months, 0 days	Ethnicity	White: British
Local Identification number	G08-123		

Reporter Details

Title	Miss	County	Greater Glasgow
First Name / Initials	A N	Postcode	G1 1RX
Surname	Other	Telephone number	141 555 5555
Reporter Profession	Nurse	Hospital / Practice Name	Somewhere PCT
E-mail Address	an.other@somewhere-pct.nhs.uk		
House Number	Green Grove Clinic	Date	14/10/2008
Address	10 Green Grove		
Address 2			
Address 3			
Town	Glasgow		

8.

Your contact details must be provided. These are held in strict confidence, and are only used to contact you when additional information is required. The details are not provided to any third party.

What will happen next?

You will then receive an acknowledgment of your report, and remember: your report is helping to safeguard public health.

Hot topic

Recent observational studies have suggested a possible association between insulin glargine and an increased risk of cancer. The results are not entirely consistent, and can neither confirm nor exclude a relationship between insulin glargine and cancer. Therefore, the European Medicines Agency has advised that no change in recommendations for use is required at present.

For NICE guidance on type 2 diabetes see http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11983

1 Evans JM, et al. *BMJ* 2005; **330:** 1304–05.
2 Bowker SL, et al. *Diabetes Care* 2006; **29:** 254–58.
3 Currie CJ, et al. *Diabetologia* published online July 2, 2009; DOI:10.1007/s00125-009-1440-6.
4 Smith U, Gale E. *Diabetologia* published online July 14, 2009; DOI:10.1007/s00125-009-1441-5.
5 Weinstein D, et al. *Diabetes Metab Res Rev* 2009; **25:** 41–49.
6 Shukla A, et al. *Endocr Relat Cancer* 2009; **16:** 429–41.
7 Stammberger I, et al. *Int J Toxicol* 2002; **21:** 171–79.
8 Hemkens LG, et al. *Diabetologia* published online June 30, 2009; DOI:10.1007/s00125-009-1418-4.
9 Colhoun HM, SDRN Epidemiology Group. *Diabetologia* published online July 15, 2009; DOI:10.1007/s00125-009-1453-1.
10 Jonasson JM, et al. *Diabetologia* published online July 9, 2009; DOI:10.1007/s00125-009-1444-2.

Insulin glargine: studies of possible cancer link

Insulin glargine

Insulin glargine (Lantus) is a long-acting insulin analogue—an insulin molecule that has been modified for more sustained effects after injection. It contains arginine residues at positions B31 and B32, together with a glycine substitution at A21. Insulin glargine is licensed for the treatment of adults, adolescents, or children age 6 years or older who have diabetes mellitus, where treatment with insulin is required.

In type 1 diabetes, glargine is usually given once daily as part of a basal bolus regimen. The National Institute for Health and Clinical Excellence recommends neutral protamine Hagedorn (NPH) insulin as first-line therapy for type 2 diabetes, but glargine may be indicated for those who require assistance to administer injections, or who cannot cope with twice-daily injections for other reasons, or who experience troublesome hypoglycaemia.

Diabetes and cancer

Type 2 diabetes is associated with an increased risk of certain types of cancer, including cancer of the breast, colon, and pancreas. These tumours are insulin-responsive in vitro, raising the possibility that insulin might act as a tumour growth factor. Three studies[1–3] found that metformin was associated with a lower risk of cancer than insulin or sulfonylureas. Cancer diagnosis or mortality are increased in insulin or sulfonylurea users compared with those on metformin,[2] suggesting that metformin may have an antitumour effect;[4] however, this remains to be confirmed.

Data for cancer risk with insulin glargine

Preclinical data

Some alterations to the insulin molecule increase its trophic effects, as shown in cell-culture systems, typically human mammary epithelial cells. These effects are mediated by prolonged binding to the insulin receptor or increased cross-reactivity with the insulin-like growth factor 1 receptor.[4]

Insulin glargine is partially degraded at the injection site yielding two bioactive products, suggesting that it acts to some extent as a pro-drug. However, there is substantial variation between individuals' insulin metabolism, and it is not possible to clearly extrapolate from in vitro to the in vivo situation.[4]

All new insulins are routinely screened for their effects on cell growth in preclinical evaluation. Some in vitro studies have suggested that insulin glargine may have greater mitogenicity than human insulin[5] or other insulin analogues.[6] A 2-year carcinogenicity study in rats and mice found no difference in frequency of mammary tumours between insulin glargine, NPH insulin, and control groups.[7] However, there was a high overall mortality rate, which may have affected the ability of this study to detect differences in tumour frequency between treatment groups.

Epidemiological studies

After an initial observational study[8] suggesting a possible association between insulin glargine and an increased risk of cancer, further findings[3,9,10] have been published. These studies assessed the overall risk of cancer in addition to the risk of breast cancer with insulin glargine, compared with risk in other treatment groups (some insulin and some oral therapy). The results of these retrospective observational studies are not entirely consistent, and can neither confirm nor

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exclude a relationship between insulin glargine and cancer. A summary of the main results is presented in the table below:

Table: *Studies of cancer risk for insulin glargine*

	Any malignancy, hazard ratio (95% CI)		Breast cancer, hazard ratio (95% CI)
Hemkens et al[8]	1·18 (1·08–1·28)*		Not assessed
Currie et al[3]	0·81 (0·59–1·11)†	1·14 (0·84–1·52)‡	0·86 (0·42–1·75)§
Colhoun et al[9] (incident insulin cohort)	0·87 (0·63–1·21)‖		1·47 (0·59–3·64)‖
Jonasson et al[10]	1·06 (0·90–1·25)‖		1·97 (1·30–3·00)‖

Comparators: *Human insulin alone. †Long-acting human insulin; data derived to ensure consistency of comparators and are not cited in original paper. ‡Biphasic human insulin; data derived to ensure consistency of comparators and are not cited in original paper. §All insulins. ‖Non-glargine insulin.

The four studies[3,8–10] were relatively short in duration of exposure and observation period to study drug-induced or drug-modified malignances. The mean follow-up for glargine varied from 1·31 years to 2·74 years, whereas the mean follow-up for comparator groups varied from 1·68 years to 3·36 years. A positive association between insulin glargine and any malignancy was found in the study by Hemkens and colleagues[8] only after re-analysis of the data for dose-related effects. Jonasson and colleagues[10] investigated the incidence of in situ tumours, breast cancer, gastrointestinal cancer, and prostate cancer and found a positive association with use of insulin glargine alone and breast cancer.

Methodological problems identified in these studies included potential exposure misclassification, selection bias, differing choice of comparator group, adjustment for confounding factors, and incomplete information on risk factors. Although the studies controlled for some confounding factors such as age and smoking, most known risk factors for breast cancer (ie, age at menopause, parity, exogenous hormone use, genetic predisposition or family history, body-mass index, and socioeconomic status) were not taken into account in most of the analyses.

Randomised controlled trials

A post-hoc analysis of data from a randomised controlled trial[11] is more reassuring. This relatively small 5-year trial compared the risk of diabetic retinopathy in patients receiving insulin glargine or NPH insulin; cancer risk was a secondary outcome. 514 patients received insulin glargine and 503 patients received NPH. Three (0·6%) patients in the insulin glargine group developed breast cancer versus five (1%) patients in the NPH group.

11 Rosenstock J, et al. *Diabetologia* published online July 16, 2009; DOI 10.1007/s00125-009-1415-7.

Advice from the European Medicines Agency

After a review of the available preclinical and clinical data, the European Medicines Agency has advised that no change in recommendations for use is required at present, and patients being treated with insulin glargine can continue their treatment. However, further research is needed in this area.

See http://www.emea.europa.eu/humandocs/PDFs/EPAR/Lantus/47063209en.pdf

Further review and research

A range of options for further research on this issue is being considered. There is a large ongoing randomised controlled trial (called ORIGIN, Outcome Reduction with Initial Glargine Intervention), which may provide additional useful information on this issue.

See also information from the National Prescribing Centre on this topic: http://www.npci.org.uk/blog/?p=374

Diabetes UK offers information for people with diabetes: see http://www.diabetes.org.uk/

Hot topic

Pseudoephedrine and ephedrine: update on measures to reduce risk of illicit use

See Drug Safety Update October 2008, p 6; www.mhra.gov.uk/mhra/drugsafetyupdate

Nasal decongestants that contain pseudoephedrine or ephedrine: risk of misuse

Pseudoephedrine and ephedrine are medicines used as nasal decongestants. There has been increasing concern that these active substances can be extracted from over-the-counter (OTC) medicines and used in the illegal manufacture of the Class A controlled drug methylamphetamine (crystal meth).

Action to minimise risk

In 2007, the MHRA conducted a public consultation exercise on a proposal to reclassify OTC medicines containing pseudoephedrine or ephedrine to prescription only medicines (POM). After the consultation, the Commission on Human Medicines (CHM) advised that the pack size for OTC products containing pseudoephedrine or ephedrine should be restricted, and that there should be a restriction to one pack per sales transaction. CHM also advised that products containing pseudoephedrine or ephedrine should be reclassified from pharmacy (P) to POM in 2 years' time (in July 2009) unless the risk of misuse in the illicit manufacture of methylamphetamine was contained.

A CHM Working Group on pseudoephedrine/ephedrine was also set up to advise CHM on the implementation of measures to minimise misuse of these medicines. The Working Group established links with pharmacy bodies (the Royal Pharmaceutical Society of Great Britain [RPSGB], the National Pharmacy Association, the Company Chemists Association); and with the Home Office, the Advisory Council on the Misuse of Drugs, the Association of Chief Police Officers, and the Serious Organised Crime Agency.

Sales restrictions

On April 1 2008, the following legal sales restrictions came into force:

- It became illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It became illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It became illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction

Professional guidance

Furthermore, the RPSGB issued professional guidance, advising that the sale and supply of products that contain pseudoephedrine or ephedrine must be made by a pharmacist or suitably trained pharmacy staff under the supervision of a pharmacist.

See http://www.rpsgb.org/pdfs/psephguide.pdf

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July 2009 review of impact of these measures

In July 2009, CHM considered a report from its Working Group on pseudoephedrine/ephedrine, which presented an update on the impact of the measures implemented to contain misuse of these medicines. CHM was asked to advise on whether small packs of medicines that contain pseudoephedrine or ephedrine should continue to be available as pharmacy medicines.

A public version of this report is available from http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON052059

The report highlighted that following implementation pharmacies have seen a 25% drop in the number of pseudoephedrine tablets or capsules being sold. The report also showed that the pharmacy sector had taken steps to improve education and awareness of misuse.

The Advisory Council on the Misuse of Drugs, the Association of Chief Police Officers, and the Serious Organised Crime Agency supported the range of measures in place and considered that they were proportionate. The Advisory Council also noted no change in the scale of methylamphetamine misuse since 2007.

CHM conclusions

In light of the report, CHM agreed with its Working Group that medicines that contain pseudoephedrine or ephedrine may continue to be sold as pharmacy medicines, provided the measures put in place to contain misuse continue to be effective (see green box above).

CHM recommended that the present level of monitoring of misuse, education of pharmacists, and liaison with relevant bodies should be maintained. They also recommended that the Working Group be reconstituted to review the situation as necessary, and in any case on a yearly basis.

Advice for pharmacists:

- Note the legal position for the sale or supply of pseudoephedrine and ephedrine (see green box, above)
- Adhere to professional guidance from the RPSGB (as outlined above)

Hot topic

Over-the-counter painkillers containing codeine or dihydrocodeine

New warnings and tighter controls on the sales of over-the-counter (OTC) medicines containing codeine or dihydrocodeine (DHC) are being introduced to minimise the risk of overuse and addiction to these medicines, in line with recent advice from the Commission on Human Medicines (CHM). The package of measures includes changes to indications, labels and leaflets, pack size, and advertising.

This action is being taken in parallel with the Department of Health's review of policy on addiction to prescription and OTC medicines.

The CHM's predecessor, the Committee on Safety of Medicines, considered the risk of addiction to OTC medicines containing codeine and DHC in 2005. At that time warnings were added to product information and pack sizes were reduced.

Feedback from patient groups has indicated that the existing warnings of the risks of addiction and overuse headache have not proved effective. Also, analysis of sales data has shown that pharmacists appear to be selling more packs of 100 effervescent paracetamol and codeine products since the reduction in pack size of the other forms.

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Key information

Indications

All indications related to colds, flu, 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) and Labels

The PIL and Labels will state that the products are for short term use only, for the treatment of moderate, acute pain, and that the products can cause addiction or overuse headache if used continuously for more than three days. The following warning will appear 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 packs greater than 32 of codeine or DHC containing OTC medicines, including effervescent formulations, will no longer be available as P products.

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'.

Timing and action required

Changes to Marketing Authorisations will be completed by 31 December 2009 and all products with the updated information will be on pharmacy shelves 3–6 months later. Existing packs of greater than 32 effervescent tablets and marked for dispensing purposes should be supplied only in accordance with RPSGB guidance.

Key messages for pharmacists:

You are asked to support the public health measures taken by:

- recommending codeine or DHC containing products appropriately within the OTC analgesic range
- giving key safety messages regarding short-term use and avoidance of addiction if taken as recommended
- noting that packs of more than 32 tablets are for dispensing use only

Monitoring

The MHRA will monitor the effect of this package of measures, reviewing sales data and ADR reports at 6 months and 12 months after amendment of the Marketing Authorisations, and will take further action if necessary.

Stop press

Clopidogrel and proton pump inhibitors: interaction—clarification

See Drug Safety Update July 2009, p 6; www.mhra.gov.uk/mhra/drugsafetyupdate

The original article in the July issue (p 2) stated that concomitant use of other medicines that inhibit CYP2C19 would also be expected to reduce the efficacy of clopidogrel and should be avoided; cimetidine was listed as a medicine that inhibits CYP2C19.

Therefore, the section on 'alternative gastrointestinal therapies' should have read:

"On the basis of pharmacokinetic data, other medicines for the treatment of gastrointestinal disorders (such as H_2 blockers, with the exception of cimetidine, or antacids) would not be expected to interact with clopidogrel. However, there are currently no substantial data from clinical-outcome studies to support this."

Other information from the MHRA

Patient Information Leaflet of the month: Hyalgan

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **Hyalgan**, which contains sodium hyaluronate and is indicated for treatment of osteoarthritis of the knee. The leaflet includes disease-related information, which helps put the rest of the leaflet in context and which in testing patients found helpful.

Access PIL of the Month at: http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines

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