

Drug Safety Update



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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Drug safety advice this month relates to new medicines that are first in their class. Information about the safety profile of these new medicines is vital to ensuring that their benefits continue to outweigh any risks. Rimonabant is a selective antagonist of cannabinoid type-1 receptors for the adjunctive treatment of obesity in some adults. Up to 10% of patients treated with rimonabant may develop depressive reactions. In light of these data, we have advice for healthcare professionals (p 2). Exenatide is an incretin mimetic that is indicated as an adjunctive treatment to improve glycaemic control in some patients with type 2 diabetes. Review of spontaneous reports has shown that acute pancreatitis may occur rarely in association with exenatide; read more on page 5.

Please use the Yellow Card Scheme to report any suspected adverse drug reaction to new medicines, which carry a black triangle to show that they are under intensive monitoring. If in doubt, please report. The Yellow Card Scheme update this month highlights how you can use our website to find out about suspected adverse drug reactions that have been reported to us (p 6). Remember that we also like to hear about any suspected serious reactions to established medicines, and our Hot topic this month on the safety of antiretrovirals highlights the importance not only of the role of these established medicines in treating HIV but also of continuously monitoring their safety. At the same time, the often expedited development of urgent new treatments for diseases such as HIV highlights the importance of monitoring the safety of a medicine when it first becomes available (p 7).

You can find more about the Scheme, and complete a Yellow Card online, at www.yellowcard.gov.uk

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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.

Drug safety advice

Rimonabant (Acomplia): depression; psychiatric adverse reactions

Keywords: rimonabant, Acomplia ▼, obesity, overweight, diabetes, psychiatric disorders, adverse drug reactions, depression, antidepressants, mood disorder

Depressive reactions may occur in up to 10% of patients treated with rimonabant. Rimonabant is contraindicated in patients with ongoing major depression or those taking antidepressants. Prescribers are encouraged to take a detailed history from patients before prescribing rimonabant to assess risk factors for psychiatric reactions, particularly depression. However, depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself

Rimonabant (Acomplia ▼) is a selective antagonist of cannabinoid type-1 (CB1) receptors. It is indicated in adults as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m²), or overweight patients (BMI >27 kg/m²) who have associated risk factors such as type 2 diabetes or dyslipidaemia. The recommended dose is one 20 mg tablet daily.

Rimonabant was approved throughout the European Union in June 2006. Important risks that were identified during clinical development were depressive disorders, anxiety, sleep disorders, and sensory neurological disturbances. Populations for which there were inadequate data to make an assessment of risk at the time of approval were: children younger than 18 years; patients older than 75 years; pregnant and nursing women; patients of African-American or Asian ethnic origin; patients with hepatic or renal impairment; and patients who were taking concomitant antidepressants or potent CYP3A4 inhibitors.

The UK, Germany, and France are the highest consumers of rimonabant worldwide; at present, it is not authorised in the USA. From launch until the end of 2007, the total amount of rimonabant dispensed in the UK equates to about 21 000 patient-treatment-years.

Psychiatric adverse effects

Psychiatric adverse drug reactions (ADRs), particularly depression, were identified as the main safety issue at the time of rimonabant's approval. In June 2007, psychiatric ADRs were reassessed, leading to new contraindications in patients with major depressive disorder or those taking antidepressants. Suicidal ideation and aggressiveness were added as ADRs to the prescribing information. Prescribers were warned that treatment with rimonabant should be stopped if a patient develops depression.

Access a European Public Assessment Report for rimonabant for a summary of the evidence and procedural steps taken for this medicine before and after its approval. See <http://www.emea.europa.eu/humandocs/Humans/EPAR/acomplia/acomplia.htm>

Access the Summary of Product Characteristics for rimonabant at <http://emc.medicines.org.uk>

UK spontaneous ADRs

Up to the end of January 2008, 673 ADR reports (reporting 1971 individual reactions) had been received with rimonabant in the UK, 423 of which were serious. Four reports had a fatal outcome (one completed suicide, one sudden death of unknown cause, and two cases of myocardial infarction).

The most common reported ADRs, which are labelled in the Summary of Product Characteristics, were:

- Psychiatric disorders (depression, anxiety, nervousness, irritability, sleep disorders, parasomnias)
- Nervous-system disorders (memory loss, dizziness, hypoaesthesia, paraesthesia)
- Gastrointestinal disorders (nausea, diarrhoea, vomiting)
- General disorders (fatigue, asthenia)
- Skin and subcutaneous disorders (pruritus, sweating)

Psychiatric reactions

876 psychiatric reactions were reported (44% of all 1971 reported reactions). The most common psychiatric reactions were depression and related disorders of mood and associated symptoms. 52 reactions involved suicidal and self-harming thoughts or behaviours, most of which were suicidal ideations (42 reports).

Depressive reactions remain a source of concern. The MHRA has received 211 UK spontaneous case reports up to the end of January 2008 that contain at least one event consistent with depression and related mood disorders. Time to onset could be estimated for 137 (65%) case reports. A third of the case reports for which time to onset is available occurred within the first week of starting treatment with rimonabant, and almost a half of these reactions occurred within the first 2 weeks. 20 of the 211 patients were receiving concomitant treatment with antidepressants (ten with SSRIs, four with venlafaxine, three with trazodone, and three with amitriptyline). 36 of the 211 patients were reported to have a history of depression or suicidality.

Other important safety signals

The following suspected ADRs, which are not labelled in the product information for rimonabant, have been identified as new safety signals based on spontaneous cases reported to MHRA up to the end of January 2008.

- Hypoglycaemic reactions
Many patients who receive rimonabant are diabetic. There have been seven reports of hypoglycaemia/decreased blood glucose. This type of reaction may be due to inadequate monitoring of blood-glucose control in patients who have managed to reduce calorie intake without appropriate adjustment of oral antidiabetics (and possibly insulin)

- Paranoia

Paranoia has been reported alone and in association with depression (15 reports).

- Rash

We have received a small number of reports of rash, including one case with a positive rechallenge

- Tremor and headache

Tremor (14 reports) and headache (40 reports) have been identified as potential ADRs

Complete a Yellow Card online at www.yellowcard.gov.uk

Please report all suspected adverse reactions to rimonabant using the Yellow Card Scheme.

The National Prescribing Centre's e-Learning platform, NPCi, has a range of materials on the obesity floor in its virtual building. For example, see http://www.npci.org.uk/therapeutics/therap/obes/knowledge_laboratory/knowledge_laboratory_quiz1.php; there are also links to key national documents on obesity from NICE, Department of Health, and the National Audit Office on the same 'floor'.

Advice for healthcare professionals:

- Depressive reactions may occur in up to 10% of patients treated with rimonabant
- Depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself. Evidence suggests that many patients who develop such reactions will do so within 2 weeks of starting treatment
- Rimonabant is contraindicated in patients with ongoing major depression or those taking antidepressants
- Prescribers are encouraged to take a detailed history from patients before prescribing rimonabant to assess risk factors for psychiatric reactions, particularly depression

Exenatide (Byetta): risk of acute pancreatitis

Keywords: exenatide, Byetta ▼, incretin mimetic, type 2 diabetes, pancreatitis

Spontaneous reports of acute pancreatitis have been received in association with exenatide. If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued

Exenatide (Byetta ▼), the first-in-class incretin mimetic, is a glucagon-like-peptide-1 analogue that stimulates insulin release from pancreatic β cells in a glucose-dependent manner.

Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin, with or without sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. Treatment with exenatide should be initiated at 5 μg twice daily for at least 1 month to improve tolerability. The dose can then be increased to 10 μg twice daily to further improve glycaemic control. Doses higher than 10 μg twice daily are not recommended.

Exenatide was first marketed in the European Union in November 2006. Several reports of acute pancreatitis have been received in association with exenatide use worldwide. Up to Sept 30, 2007, 89 reports of pancreatitis had been received, 87 from the USA and two from Germany. One case had a fatal outcome. A UK report of acute and chronic pancreatitis in a female given 5 μg exenatide was received in November 2007.

Advice for healthcare professionals:

- Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain; back pain may also be present
- If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued

Reporting of suspected adverse reactions to exenatide

As with all medicines, the safety of exenatide remains under close review. Please continue to report to the MHRA and the Commission on Human medicines all suspected adverse reactions to exenatide via the Yellow Card Scheme.

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions. See www.yellowcard.gov.uk

Access DAPs at <http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/Druganalysisprints/index.htm>

For more information about MedDRA see <http://www.meddramsso.com/MSSOWeb/index.htm>

Summaries of Product Characteristics and Patient Information Leaflets for a medicine can be viewed at <http://emc.medicines.org.uk/>; see also the British National Formulary (www.bnf.org).

Has this reaction been reported before? Finding out about suspected adverse drug reactions reported to the MHRA

Drug Analysis Prints (DAPs) are anonymised listings of suspected adverse drug reactions reported to the MHRA by healthcare professionals and patients through the Yellow Card Scheme. We have recently reformatted and updated all DAPs.

Every DAP lists all suspected reactions that have been reported to the MHRA during a defined period for a particular medicine by name of active ingredient. DAPs are available in pdf format on our website in the Safety Information section

DAP layout:

- A DAP for a medicine lists individually all suspected adverse reactions that have been reported for that medicine on a Yellow Card
- The end of the DAP shows the total number of suspected adverse drug reactions and total number of Yellow Card reports submitted for a particular medicine. Yellow Cards may contain more than one suspected reaction and the total number of suspected reactions listed may be higher than the number of reports received for a medicine
- Data are given for reports when the medicine was given as a single active ingredient or when it was given in a product that contained several active ingredients; for every reaction, the total number of reports are listed, as is the number with a fatal outcome
- Adverse drug reactions are listed according to MedDRA (Medical Dictionary for Regulatory Activities) classifications of System Organ Class (eg, musculoskeletal and connective tissue disorders), High Level Term (eg, muscle pains), and Reaction Name (eg, myalgia)

Interpretation of DAPs

DAPs provide a useful overview of reporting patterns for medicines and are a valuable tool that form part of our continual monitoring of the safety of medicines. Healthcare professionals may find DAPs useful—for example, to see whether a suspected adverse drug reaction for a particular medicine has been reported to us previously.

However, DAPs are not a complete account of the risks that may be associated with a medicine. Conclusions about the risks and benefits of a medicine cannot be made on the information in DAPs alone. More comprehensive information about the safety profile of a medicine can be found in the Summary of Product Characteristics or Patient Information Leaflet.

Continued on page 7

Yellow Card Scheme update

Further information can be found at <http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/YellowCarddata/index.htm>

Points to consider when using DAPs:

- Information included in DAPs cannot be used to estimate the likelihood of having an adverse drug reaction from taking a medicine because not all adverse reactions are reported and we do not know how many people have taken that medicine without having a reaction
- Reporters are asked to send a Yellow Card if they *suspect* that a medicine may have caused an adverse reaction. Therefore, the inclusion of a report for a particular reaction on a DAP does not prove that the medicine in question *caused* the reaction
- Determination of whether a particular medicine caused an adverse drug reaction is usually complex: other factors may have played a part in the reaction such as disease(s) for which the patient is receiving treatment, other medicines being taken by the patient, or a naturally occurring event or other unknown factor

Hot topic

For further information about monitoring the safety of antiretroviral drugs, see our website: <http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/index.htm>

Access European Public Assessment Reports at <http://www.emea.europa.eu/htmls/human/epar/eparintro.htm>

Monitoring the safety of antiretroviral drugs

The first antiretroviral drug, zidovudine, became available more than 20 years ago, and since then there have been substantial advances in the treatment options available to patients with HIV and in their prognosis. The advent of new drug classes and in combination therapy has not only led to important benefits for patients, but also to the need for ongoing monitoring and management of the risks associated with treatment.

The clinical need for new or improved treatments for HIV is usually perceived as urgent and most new treatments are made available for use as quickly as possible. Therefore, knowledge of a drug's safety is incomplete when it first becomes available and it is monitored closely after marketing.

Recent examples of new treatments or new formulations or combinations, of treatments, for HIV include:

- Maraviroc (Celsentri ▼): the first CCR5 inhibitor
- Raltegravir (Isentress ▼): the first integrase inhibitor
- Duranavir (Prezista ▼): a new protease inhibitor for highly pretreated patients
- Atripla: a new combination tablet of efavirenz, tenofovir, and emtricitabine

To help improve knowledge about the safety of a new medicine, a company that holds a Marketing Authorisation for it now produces a risk-management plan. A summary of the plan can be found in the European Public Assessment Report of the medicine.

Of course, safety issues are not associated with newer drugs only. As a consequence of the short-term nature (ie, actual treatment periods) of clinical trials, the long-term safety profile of all antiretrovirals is continually changing.

Hot topic

Recent examples of safety issues associated with older antiretrovirals include:

- Abacavir and didanosine: increased risk of myocardial infarction (findings from the D:A:D study; see p 9 and position statement from D:A:D steering committee at <http://www.chip.dk/portals/0/files/DAD%20Position%20statement%20CROI%202008%20FINAL%202.pdf>)
- Norvir (ritonavir): new drug interactions (eg, with buprenorphine, see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Norvir/052796en8b.pdf>)
- Crixivan (indinavir): renal failure (see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Crixivan/058996en8b.pdf>)
- Sustiva (efavirenz): gynaecomastia (see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Sustiva/076199en8b.pdf>)
- Viread (tenofovir): risk of hepatitis B reactivation after withdrawal (see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/viread/351001en8b.pdf>)
- Telzir (fosamprenavir): angioedema (see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/telzir/132504en8.pdf>)
- All antiretrovirals: osteonecrosis (see *British National Formulary* 54th edn, September 2007, section 5.3.1 HIV infection, p 325 or www.bnf.org)
- Effect of proton pump inhibitors on protease inhibitor blood levels (see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/reyataz/586503en8b.pdf> and <http://www.emea.europa.eu/humandocs/PDFs/EPAR/kaletra/453001en8b.pdf>)
- Kaletra (lopinavir with ritonavir): overdosing of neonates (see <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON2032268>)

Reporting of suspected adverse drug reactions

The Yellow Card Scheme is an important way of detecting emerging safety issues for medicines. We use reports of suspected adverse effects of drugs (or interactions with other drugs, herbal products, or food supplements) from healthcare professionals and patients or carers to determine whether information for a medicine accurately reflects its safety profile.

For all Yellow Cards we receive, it is important to note that patient and reporter confidentiality is maintained. Specific guidance on the reporting of suspected adverse reactions to antiretrovirals can be found on our website. In addition to the basic information included on a Yellow Card report, it is very helpful for our assessment of these reports to know the following:

- CD4 count
- Lowest ever CD4 count
- CD4 count at start of treatment
- HIV viral load
- Relevant test results (including baseline values)
- Drug-resistance profile
- Previous illness
- Previous side-effects

See www.yellowcard.gov.uk and Yellow Card Scheme update, p 6)

See <http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reporting suspected adverse drug reactions/Healthcareprofessionalreporting/Whattoreport/index.htm>

Stop press

Abacavir and didanosine: results of D:A:D study

1 D:A:D Study Group. *Lancet* published online April 2, 2008. DOI:10.1016/S0140-6736(08)60423-7; www.thelancet.com

Data¹ from the D:A:D study (Data collection of Adverse effects of anti-HIV Drugs) suggest an increased risk of heart attack associated with abacavir and didanosine. Relative risk of heart attack with recent use (ie, currently or within preceding 6 months) was 1.90 (95% CI 1.47–2.45) for those who took abacavir and 1.49 (1.14–1.95) for those who took didanosine compared with no recent use.

The MHRA, together with the European Committee for Medicinal Products for Human Use, have analysed data from this study and those from clinical trials provided by the maker of abacavir. These data do not enable a definitive conclusion about the association of these medicines with heart attack. Ongoing studies will further assess this potential risk.

Advice for healthcare professionals:

- Patients should not stop taking anti-HIV medicine unless instructed by their doctor; patients who have any concerns should speak to their doctor
- Healthcare professionals and patients should consider ways that the risk of heart attack can be reduced (eg, giving-up smoking, control of diabetes, and lowering of blood pressure and cholesterol)

See <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Kivexa/14288808en.pdf>

The safety of abacavir and didanosine remain under close review. Further information is available on the website of the European Medicines Agency.

Enoxaparin (Clexane) contamination: advice for healthcare professionals

We have recently been made aware that some batches of Clexane (enoxaparin) in the UK contain low levels of contamination with over-sulphated chondroitin sulphate (OSCS). There is no evidence that this level of contamination is associated with any increased risks to patients, and the Commission on Human Medicines has advised that product on the UK market can continue to be used to avoid severe supply shortages and subsequent risks to patients.

It is important that patients continue to receive Clexane as prescribed by their doctor. Purely as a precaution, healthcare professionals are advised not to administer Clexane via the intravenous and arterial line routes, and to be vigilant for any signs of severe allergic or hypotensive adverse reactions. The manufacturer has advised that supplies of Clexane without OSCS will be available from June 2008.

Please continue to report any suspected adverse reactions to enoxaparin via the Yellow Card Scheme.

Further information can be found at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/index.htm>; complete a Yellow Card online at www.yellowcard.gov.uk

Other information from the MHRA

Intrathecal drug pumps

See

<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/FieldSafetyNoticesformedicaldevices/CON2033876>

In January 2008, the MHRA placed on its website a field safety notice about an increased risk of inflammatory mass formation in patients with implantable intrathecal drug pumps. Patients who use these devices typically include those who require administration of intrathecal morphine for pain therapy or intrathecal baclofen for spasticity.

An inflammatory mass typically presents with symptoms that include decreased therapeutic response, inadequate pain relief, increased pain, and neurological deficit or dysfunction. Imaging commonly shows an inflammatory mass at, or near, the distal tip of the intrathecal catheter. A pump manufacturer has become aware of a higher than anticipated incidence of these lesions, with up to 3% of those receiving intrathecal opioid infusions being affected,¹ compared with incidences of 0.49% and 0.1% previously cited in product literature. The risk of inflammatory-mass occurrence seems to increase over time and with higher concentration of opioids; however, the susceptibility of an individual patient to an inflammatory mass cannot be predicted. There is no reason why this issue should be specific to one pump manufacturer: it seems to be related more to the infused medicine.

¹ Deer TR. *Pain Physician* 2004; **7**: 225–28.

Advice for healthcare professionals:

- Consider prompt neurosurgical consultation and imaging to confirm or exclude the diagnosis of an inflammatory mass in patients with new-onset neurological signs or symptoms
- On administration of intrathecal opioids, the lowest effective dose and concentration should be given
- Follow the patient management and system-troubleshooting guidelines that are given in the field safety corrective action
- Please report all adverse incidents related to these pumps and catheters to the MHRA

To report an adverse incident, visit www.mhra.gov.uk

Patient Information Leaflet of the month

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

New legal requirements on manufacturers require them to test Patient information leaflets (PILs) with potential patients. User-testing makes sure that the presentation of the information enables patients to find and understand key messages for safe and effective use of the medicine. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in this series is the PIL for **Vicks Sinex Soother Nasal Spray**—an over-the-counter medicine used to relieve the symptoms of blocked nose associated with colds and sinus problems. This PIL was approved as part of a European procedure.

Pregnancy testing: top tips leaflet

Download the leaflet at <http://www.mhra.gov.uk/Publications/Postersandleaflets/CON014278>

We have produced a leaflet to help ensure best practice for pregnancy testing by healthcare professionals. We have investigated reports of false results with pregnancy tests kits, sometimes due to handling of samples and interpretation of results. The leaflet may be of particular interest to point-of-care coordinators and GPs.

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

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