# 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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## Contents



The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency 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.

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In our first article, we communicate on the potential increased risk of congenital malformations with the narcolepsy medicine modafinil (page 2).

Second, due to cases of serious liver injury reported with pirfenidone for idiopathic pulmonary fibrosis, we ask healthcare professionals to test liver function promptly in patients who report symptoms or have clinical signs of liver injury. Follow new recommendations on page 5 to adjust the dose or discontinue treatment.

On page 8, we inform of new monitoring requirements with the intravenous iron ferric carboxymaltose (Ferinject▼) following reported cases of symptomatic hypophosphataemia leading to infrequent reports of osteomalacia and consequential fractures. Monitor phosphate levels in patients with risk factors or those requiring high or long-term doses of ferric carboxymaltose (page 8).

On page 11, we inform of cases of serotonin syndrome in patients using the smoking cessation medicine bupropion (Zyban) with serotonergic medicines (page 11). Advise patients who are on concomitant serotonergic medicines of the signs and symptoms of serotonin syndrome, including mild early signs, and instruct them to seek medical advice if these occur.

In the final article, see page 14 for how to contribute views and information to an expert review of isotretinoin and suspected association with psychiatric and sexual disorders.

# Modafinil (Provigil): increased risk of congenital malformations if used during pregnancy

Modafinil potentially increases the risk of congenital malformations when used in pregnancy. Modafinil should not be used during pregnancy and women of childbearing potential must use effective contraception during treatment and for 2 months after stopping modafinil.

### Advice for healthcare professionals:

- modafinil potentially increases the risk of congenital malformations (including congenital heart defects, hypospadias, and orofacial clefts); modafinil should not be used in pregnancy and alternative treatment options for narcolepsy should be considered
- women of childbearing potential must use effective contraception during treatment and for 2 months after stopping modafinil
- modafinil may reduce the effectiveness of steroidal contraceptives, including oral contraceptives, therefore alternative or concomitant methods of contraception are required – see Advice on contraception use on page 3
- ensure all female patients of childbearing potential taking modafinil are informed and fully understand that:
    - modafinil should not be used during pregnancy due to the increased risk to the fetus
    - effective contraception is needed during treatment with modafinil and for 2 months after stopping modafinil treatment
    - they should discuss plans for pregnancy early with their doctor and continue contraception for 2 months after stopping modafinil
- report any suspected adverse reactions experienced by a woman or child associated with medicines taken during pregnancy via the Yellow Card Scheme

## Review of safety in pregnancy

Modafinil (Provigil, generics) is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy (see full indication in summary of product characteristics). Narcolepsy is a rare long-term brain condition that causes excessive daytime sleepiness, cataplexy (loss of muscle tone), and sleep disturbance. Recommended supportive measures for narcolepsy symptoms include behaviour modifying measures, sleep hygiene, and scheduled daytime naps.

A European review concluded that there was a possible increased risk of congenital malformations in the children of women treated with modafinil during pregnancy. The product information, including the patient information leaflet, has been updated and a letter sent to prescribers of modafinil in January 2020.

The review considered data from a prospective US registry and spontaneous reports of major congenital malformations including congenital heart defects, hypospadias, and orofacial clefts, for which causal relationship with modafinil was considered possible. The MHRA has considered the European review and other safety data,[1] which support the suggestion of an increased risk of major congenital malformations with use of modafinil in pregnancy.

1. Damkier P et al. JAMA 2020; 323: 374–76.

## Data for risk of congenital malformations

The Nuvigil and Provigil registry, a prospective, observational study in the USA, was established in 2010 to characterise the pregnancy and foetal outcomes associated with exposure to modafinil and related drug armodafinil from 6 weeks before conception and/or during pregnancy.

Interim data ascertained from the 2018 Annual Registry report (considered by the review that led to the most recent changes to product information) estimated that the prevalence of major congenital malformations was approximately 14.75% (95% CI 5.85–23.65), compared with 3% in the general population. The estimated prevalence of cardiac anomalies of 4.92% (0–10.34) was also higher than reported in the general population (1%). These rates are based on prospective data from 78 pregnancy cases; 61 of these reported a live birth outcome, of which 9 presented with major congenital anomalies (including 3 cardiac congenital anomalies). While the target sample size for the registry has not yet been reached, this interim analysis has shown that the prevalence of major congenital malformations is above the background rate in the general population. In addition to the registry findings, studies in animals have shown reproductive toxicity.

## Advice on contraception use

Before starting modafinil, women of childbearing potential must be informed of the risk of teratogenicity. Patients must use effective contraception during treatment with modafinil and for 2 months after stopping.

Modafinil may reduce the effectiveness of steroidal contraceptives, including oral contraceptives, through the induction of CYP3A4/5.[2] Alternative or concomitant methods of contraception are required.

Guidance is available on interactions with contraception from the Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit (January 2017, last reviewed 2019). For enzyme-inducing medicines such as modafinil, the guidance recommends avoiding combined hormonal contraception (CHC) pills, rings, and patches; progestogen-only pill; progestogen-only implants; and ulipristal acetate emergency contraception.

The guidance states that suitable long-term methods are copper intrauterine device (copper IUD), levonorgestrel-releasing intrauterine system (LNG-IUS), and depot progestogen-only injections. For emergency contraception, if a copper IUD is not suitable, a double dose of oral levonorgestrel emergency contraception is advised – see the product information for levonorgestrel.

The guidance recommends that if use of modafinil is only anticipated for a short time (2 months), barrier methods in conjunction with existing contraceptives may be advised. When using any medicine with teratogenic potential, a woman should be advised of the risks and encouraged to use the most effective contraceptive method taking into account her personal circumstances. See Drug Safety Update March 2019 for guidance on contraceptive methods and frequency of pregnancy testing to reduce inadvertent exposures during pregnancy in a woman taking a medicine of teratogenic potential.

Women of childbearing potential planning a pregnancy should be advised on the need to discuss other narcolepsy treatment options with their doctor before stopping contraception.

2. Robertson P Jr and others. Clin Pharmacol Ther 2002; 71: 46–56

## Report on a Yellow Card

Please continue to report any suspected adverse drug reactions (ADRs) associated with modafinil or any other medicines via the Yellow Card scheme.

Please report any suspected ADRs associated medicines taken during pregnancy or breastfeeding experienced by the woman and any suspected effects on the baby or child.

All patients, caregivers, and healthcare professionals can report a Yellow Card when they suspect a medication used during pregnancy has caused an adverse reaction or adverse pregnancy outcome.

When reporting ADRs related to medicines used in pregnancy, the following information is particularly valuable for our assessment of the report:

- Timings of when the medicine was taken during the pregnancy
- The outcome of the pregnancy (when known)
- Details of any relevant family history, including any obstetric history
- For reports concerning congenital malformations, a detailed clinical description of any congenital anomaly and the results of any imaging (for example, scans), or laboratory tests

Please include any other relevant information; including other medications or substances taken during the pregnancy, as well as folic acid intake.

Report Yellow Cards using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

*Article citation: Drug Safety Update volume 14, issue 4: November 2020: 1.*

# Pirfenidone (Esbriet): risk of serious liver injury; updated advice on liver function testing

Serious liver injury has been reported during treatment with pirfenidone in the first year after initiation, including 2 cases with a fatal outcome. Measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels before starting pirfenidone treatment, monthly for the first 6 months of treatment, and then every 3 months thereafter.
Follow new guidance on testing liver function promptly in patients who report symptoms or have clinical signs that might indicate they have liver injury and adjust the dose or discontinue treatment according to new recommendations.

**Advice for healthcare professionals:**

- serious cases of drug-induced liver injury, including liver failure, have been reported in patients treated with pirfenidone; cases have been estimated to be of uncommon frequency but 2 reports worldwide had a fatal outcome
- continue to monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels before initiation, at monthly intervals during the first 6 months of treatment and every 3 months thereafter
- advise patients to seek medical help immediately if they have signs and symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice
- perform prompt clinical evaluation and measure liver function in patients who report symptoms that may indicate liver injury
- in the event of significant elevation of liver enzymes or clinical signs and symptoms of liver injury, adjust the dose of pirfenidone or discontinue treatment (see table on page 7 for new guidance)
- monitor closely for signs of toxicity if pirfenidone is being used concomitantly with inhibitors of one or more other CYP isoenzymes involved in the metabolism of pirfenidone (see table)
- report suspected adverse reactions associated with pirfenidone to the Yellow Card scheme

## Review of reports of severe liver injury

Pirfenidone (brand name Esbriet) is an anti-fibrotic and anti-inflammatory agent indicated for the treatment of idiopathic pulmonary fibrosis. Pirfenidone is known to commonly cause elevation of liver transaminases (ALT and AST), with associated concomitant increases in bilirubin in rare cases.

A recent European review of safety data identified severe cases of drug-induced liver injury associated with pirfenidone reported post-marketing, including isolated cases with a fatal outcome. Reported events included hepatitis, liver injury, and liver failure.

Reports of serious liver injury are considered to be uncommon (may occur in between 1 in 100 and 1 in 1000 people who take pirfenidone) and the benefit-risk profile of pirfenidone in the approved indications remains favourable. Although the aetiology is unclear, idiosyncratic reactions may underlie the occurrence of drug-induced liver injury following treatment with pirfenidone.

## New advice to minimise risk

Following the findings of the review, existing warnings for the potential for hepatotoxicity in the product information will be strengthened to include the risk of clinically relevant drug-induced liver injury with pirfenidone. While the recommendation for liver function monitoring before and during treatment has not changed, new advice will be added to minimise risk in patients taking pirfenidone.

New warnings in the summary of product characteristics will ask for prompt liver function testing in patients who report symptoms or have clinical signs that might indicate liver injury, and adjustment of the dose of pirfenidone or discontinuation of treatment if necessary – see Table.

A letter has been sent to prescribers to advise them of this information and updates have been made to the educational materials and the prescriber checklist to reflect the new advice. A targeted questionnaire has also been introduced, which will be used by the marketing authorisation holder for pirfenidone to follow up with healthcare professionals to obtain further details of reported cases of serious hepatic reactions.

## Details of fatal reports

Two fatal cases consistent with drug-induced liver injury were reported in the literature in association with pirfenidone.[1,2] These events of drug-induced liver injury and subsequent liver failure occurred at 1 month and 12 months after initiation of treatment with pirfenidone.

In the first case, the patient presented with acute liver failure and grade 3 hepatic encephalopathy, accompanied by elevated liver function test results, jaundice, and altered mental state.[1] Pirfenidone was withdrawn but the patient, who had no other apparent causes for acute liver failure, subsequently had organ failure and died. Post-mortem liver biopsy revealed findings consistent with drug-induced liver injury.

In the second fatal case, the patient developed elevated transaminases after 1 year of pirfenidone treatment and 3 days after starting concomitant treatment with esomeprazole.[2] Despite discontinuation of both medicines, the patient was hospitalised with jaundice, pruritus, nausea, and fatigue accompanied by further increase in transaminases. Liver biopsy indicated drug-induced liver injury and the patient died from sepsis, lactic acidosis, and multiorgan failure. Esomeprazole is a known substrate for cytochrome P450 enzymes that are important in pirfenidone metabolism, and the authors of the study hypothesise that this could lead to a potential drug-drug interaction.[2]

1 Verma N and others. Hepatol Commun 2017; 2: 142–147.

2 Benesic A and others. Hepatology 2019; 70: 1869–71.

## Recommended liver monitoring

Perform liver function tests (ALT, AST, and bilirubin) before initiating treatment with pirfenidone, and subsequently at monthly intervals for the first 6 months. and then every 3 months thereafter.

Clinically evaluate and perform liver function tests in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of hepatic injury, adjust the dose or discontinue treatment according to the guidance.

## Table – Dose adjustments due to liver enzyme abnormalities

The dose adjustments due to liver enzyme abnormalities or clinical signs and symptoms have been updated in the product information and the new recommendations are below.

| Laboratory value of aminotransferases by upper level normal (ULN) | Actions to take |
|---|---|
| 3–5-times ULN without bilirubin elevation | • Exclude other causes<br>• Monitor the patient closely<br>• Consider discontinuing other medicines associated with liver toxicity<br>• Consider possible drug interactions if the patient is taking inhibitors of CYP isoenzymes involved in the metabolism of pirfenidone – for example, fluvoxamine (CYP1A2), amiodarone (CYP1A2 and CYP2C9), chloramphenicol (CYP2C19), and fluoxetine (CYP2D6)<br>• Reduce or interrupt the dose of pirfenidone if clinically appropriate<br>• Re-escalate pirfenidone to the recommended daily dose if tolerated once liver function tests are within normal limits |
| 3–5-times ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury | Permanently discontinue pirfenidone therapy; do not reinitiate treatment |
| Higher than 5-times ULN | Permanently discontinue pirfenidone therapy; do not reinitiate treatment |

## Further information on hepatic risks

During clinical development of pirfenidone, an increased cumulative incidence of hepatic treatment-emergent adverse events was observed; most of which were laboratory abnormalities without clinical signs and symptoms. Pirfenidone is contraindicated in patients with severe or end-stage hepatic disease.

## Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions (ADRs) to the Yellow Card Scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

*Article citation: Drug Safety Update volume 14, issue 4: November 2020: 2.*

## Ferric carboxymaltose (Ferinject▼): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures

Monitor serum phosphate levels in patients treated with multiple high-dose administrations, or those on long-term treatment, and in those with pre-existing risk factors for hypophosphataemia. Re-evaluate ferric carboxymaltose treatment in patients with persistent hypophosphataemia.

**Advice for healthcare professionals:**

- ferric carboxymaltose is known to be commonly associated with hypophosphatemia
- cases have been reported of symptomatic hypophosphataemia leading to infrequent reports of hypophosphataemic osteomalacia and fractures in patients with existing risk factors and following prolonged exposure to high doses – some cases required clinical intervention, including surgery
- monitor serum phosphate levels in patients:
    - requiring multiple administrations of ferric carboxymaltose at higher doses
    - on long-term treatment with ferric carboxymaltose
    - with pre-existing risk factors for hypophosphataemia such as vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, inflammatory bowel disease, and osteoporosis
- advise patients to seek medical advice if they experience symptoms indicative of hypophosphataemia, including new musculoskeletal symptoms or worsening of tiredness – be aware these symptoms may be confused with those of iron deficiency anaemia
- if hypophosphataemia persists, re-evaluate treatment with ferric carboxymaltose
- report all suspected adverse drug reactions to ferric carboxymaltose to the Yellow Card scheme without delay

### Review of risk of hypophosphataemia and osteomalacia

Ferric carboxymaltose (Ferinject▼) is indicated for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used and there is a clinical need to deliver iron rapidly.

Ferinject has been associated with common cases of hypophosphatemia (low blood phosphate).

A recent European review concluded that ferric carboxymaltose is associated with hypophosphataemic osteomalacia (inadequate mineralisation of the bone matrix leading to softening of the bones). The review recommended strengthened advice to make healthcare professionals aware that osteomalacia can be a consequence of hypophosphataemia and to ensure early detection and effective management of hypophosphataemic osteomalacia.

Based on the available data, it is difficult to estimate the magnitude of the risk of hypophosphataemic osteomalacia with ferric carboxymaltose, therefore the risk of this adverse reaction is included in the product information with a frequency category of not known.

### Cases of osteomalacia in post-marketing use

As of 14 February 2020, the review considered 36 spontaneous cases worldwide (in patients with concurrent hypophosphataemia associated with ferric carboxymaltose. Osteomalacia was reported in 28 cases and hypophosphataemic osteomalacia in 6 cases, with 2 cases reporting both terms. As of February 2020, the worldwide estimated exposure to ferric carboxymaltose was estimated to be 12,491,000 patient-years (168,632,771 defined daily doses).[1]

In most cases (30 [83%]) hypophosphataemia was reported as medically significant (moderate to severe) using a phosphate cut-off of lower than 2.0 milligram per decilitre. Where reported the patient age was 26–39 years in 8 cases, 40–56 years in 12 cases, 57–68 years in 4 cases, and 73–81 years in 3 cases.

Where dosing information was reported, 13 patients had been given doses of 1000mg per infusion of ferric carboxymaltose for an average of 19 infusions over a period of 5–24 months. The time to onset of osteomalacia after starting treatment with ferric carboxymaltose at 1000mg dose was reported in 6 cases and ranged from 3 months to 5 years (median 14.5 months).

Of the 36 cases, 24 cases reported one or more reliable diagnostic criteria for osteomalacia: alkaline phosphatase (12 cases), parathyroid hormone (12 cases), magnetic resonance imagery (11 cases), bone scan (5 cases), bone biopsy (3 cases), and bone densitometry (2 cases).

All 36 cases presented with one or more risk factors for osteomalacia, namely inflammatory bowel disease (14 cases), vitamin D deficiency (9 cases), osteoporosis (8 cases), malabsorption (6 cases), Rendu-Osler disease (6 cases), hyperparathyroidism (6 cases), long-term steroid use (6 cases), and chronic use of antacid therapies (3 cases).
Approximately half of the patients (19 of 36; 53%) developed one or more fractures (where reported, femoral neck fracture or pelvic or hip fracture) in conjunction with osteomalacia.

Where reported, the outcome for the patient was recovered in 7 cases and recovering in 9 cases. The patients were treated with phosphate, calcium and/or vitamin D supplements. Where required, surgical treatment was provided for fractures.

In the UK up to 22 October 2020, we have received 28 Yellow Card reports of hypophosphataemia and 2 reporting cases of hypophosphataemic osteomalacia with Ferinject. These UK cases were considered as part of the EU review.

### Mechanisms and risk with other irons

Intravenous iron products are indicated for the treatment of iron deficiency and anaemia when oral iron supplements cannot be given or have not worked.

Hypophosphataemia (of uncommon frequency) is a listed adverse effect in association with Monofer▼ (iron isomaltoside, now known as ferric derisomaltose) – letter to healthcare professionals about name change.

Up to 1 January 2020, although cases have been reported of hypophosphatemia (including some serious cases), we are not aware of any cases reported of hypophosphataemic osteomalacia in association with ferric derisomaltose worldwide. As of February 2020, ferric derisomaltose has a worldwide exposure of 3,216,000 patient-years (based on a defined daily dose of 100mg iron equivalent).[2] Up to 22 October 2020, the Yellow Card scheme has received 2 reports of hypophosphataemia with Monofer and we are not aware of any cases of osteomalacia.

The risk of persistent hypophosphatemia and osteomalacia may be higher with ferric carboxymaltose than with other intravenous iron formulations. A key mechanism postulated is that the carbohydrate moieties in ferric carboxymaltose may disproportionately inhibit degradation of fibroblast growth factor 23 (FGF23),[3,4] which can result in increased FGF23 activity and ultimately greater renal phosphate wasting.[5]

## Report any suspected adverse reactions

Intravenous iron medicines are black triangle medicines (▼) and any suspected adverse drug reactions (ADRs) should be reported to the Yellow Card scheme.

Reporting suspected ADRs, even those known to occur, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

*Article citation: Drug Safety Update volume 14, issue 4: November 2020: 3.*

# Bupropion (Zyban): risk of serotonin syndrome with use with other serotonergic drugs

Cases of serotonin syndrome have been identified in associated with bupropion, especially in overdose or when bupropion is administered with other drugs with a serotonergic effect.

**Advice for healthcare professionals:**

- cases of serotonin syndrome have been reported in association with bupropion and coadministration with serotonergic drugs, for example
    - selective serotonin reuptake inhibitors (SSRIs)
    - serotonin norepinephrine re-uptake inhibitors (SNRI)
- if concomitant prescribing with other serotonergic drugs is clinically warranted:
    - do not exceed the recommended dose
    - remind patients of the milder symptoms of serotonin syndrome at initiation of treatment and at any change of dose and the importance of seeking medical advice if they occur
- if serotonin syndrome is suspected, either decrease the dose of bupropion or withdraw therapy depending on the severity of the symptoms

**Advice to give to patients**

- if you are told you may be at risk of serotonin syndrome, be aware of symptoms, including mild signs such as nausea, vomiting, and diarrhoea or increased heart rate and agitation (see full list below) and talk to your prescriber if you experience these
- never exceed the prescribed dose of bupropion
- always read the patient information leaflet for side effects to be aware of and when to seek medical advice

## Review of cases of serotonin syndrome

Bupropion (Zyban) is indicated as an aid for smoking cessation in combination with motivational support in nicotine-dependent patients. It is also authorised in combination with naltrexone (Mysimba▼) as an adjunct to a reduced-calorie diet and increased physical activity for the management of weight in adults with obesity or who are overweight with co-morbidities.

A recent European review of safety data for Zyban identified at least 8 cases of serotonin syndrome, a potentially life-threatening condition, where a possible interaction between bupropion and a serotonergic drug was thought to have led to serotonin syndrome. The review also identified 6 cases with good evidence of an association with an overdose of bupropion. In the majority of these cases the patients had intentionally taken more than the prescribed dose.

The product information (summary of product characteristics and patient information leaflet) has been updated to include post-marketing reports of serotonin syndrome when bupropion is co-administered with a serotonergic agent such as selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine re-uptake inhibitors (SNRIs).

If concomitant treatment with other serotonergic agents is clinically warranted, the patient should be advised of the milder symptoms of serotonin syndrome and told to seek advice should they occur, particularly during treatment initiation and dose increases. Advice that serotonin syndrome has been reported in cases of overdose also been included in the product information.

In the UK up to October 2020, the Yellow Card scheme has received 3 reports of serotonin syndrome associated with bupropion, one of which was a potential overdose of bupropion and two of which were associated with concomitant use of antidepressant medicines.

## Serotonin syndrome – signs and symptoms

Serotonin syndrome is an iatrogenic disorder of serotonergic hyperstimulation in which the underlying mechanism is thought to involve excessive stimulation of 5-HT1A receptors. It occurs most commonly when two or more serotonergic agents with different pharmacological mechanisms are administered either concurrently or sequentially without a sufficient washout period. However, it can also be associated with a single serotonergic agent, particularly at a high dose.

Signs and symptoms of serotonin syndrome may include mental-status changes (for example, agitation, hallucinations, coma), autonomic instability (for example, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (for example, hyperreflexia, incoordination, rigidity), and gastrointestinal symptoms (for example, nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, a dose reduction or discontinuation of bupropion therapy should be considered, depending on the severity of the symptoms.

## Advice for patients

Ensure at initiation of bupropion that patients are aware that they should return for a review of their medication, especially if they are also taking medicines for depression (such as SSRI or SNRI), if they experience any of the following side effects:

- mental status changes (for example, agitation, hallucinations),
- gastrointestinal symptoms (for example, nausea, vomiting, diarrhoea
- body temperature above 38°C
- increase in heart rate
- signs of unstable blood pressure such as facial flushing, headaches, sweating, short periods of dizziness
- exaggeration of reflexes
- muscular rigidity
- lack of coordination

Early symptoms may be gastrointestinal symptoms or increased heart rate and agitation.

## About bupropion signalling pathways

Bupropion is a norepinephrine–dopamine reuptake inhibitor (NDRI). Although bupropion mainly has an effect on dopamine and noradrenaline reuptake, there is some published evidence to suggest cross-reactivity between dopaminergic, noradrenergic, and serotonergic signalling in the central nervous system.[1,2] The exact relationship between these signalling pathways remains unclear.

1. Cooper BR and others. J Pharmacol Exp Ther 1980; 215: 127–134.

2. Warner C, Shoaib M. Addict Biol 2005; 10: 219–31.

## Report to the Yellow Card Scheme

Please report medication errors resulting in harm, including overdose and accidental exposure to a medicine, or any other suspected side effects on a Yellow Card.

Your report helps to improve the safety of medicines in the UK. Never assume someone else will report an adverse drug reaction – if in doubt, report.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

*Article citation: Drug Safety Update volume 14, issue 4: November 2020: 4.*

# Isotretinoin (Roaccutane▼): contribute to expert review

A review is being undertaken by the Medicines and Healthcare products Regulatory Agency with advice from the Commission on Human Medicines and the Isotretinoin Expert Working Group due to concerns about the possible association between isotretinoin and suspected psychiatric and sexual disorders.

Isotretinoin (Roaccutane▼, Reticutan▼, and Rizuderm▼) is indicated for severe acne that is resistant to adequate courses of standard antibacterial or topical therapy. Although an effective treatment for severe acne, isotretinoin has significant risks that require specialist oversight, including teratogenic effects if pregnancies are exposed and the potential for psychiatric reactions and sexual dysfunction. We recently published a reminder of important risks and precautions.

An Expert Working Group is reviewing the available evidence relating to isotretinoin, and will advise whether the MHRA should take additional regulatory action, for example, improving the information for patients to help minimise the risks of psychiatric and sexual side effects, suspected to be associated with isotretinoin. We invite patients and their families, healthcare professionals, researchers and organisations to contribute views and information to the review.

**Contribute to the Call for information.**

Details about the call for information, including what and how to submit, are available via the consultation website.

## Call for reporting

Isotretinoin is a black triangle medicine and all suspected adverse reactions, including any sexual and psychiatric adverse reactions, should be reported via the Yellow Card scheme.

Reports can be made of suspected reactions experienced at any time, including historic adverse experiences with medicines. Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset, treatment dates, and product brand name should also be included.

Report to the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

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# Letters and drug alerts sent to healthcare professionals in October 2020

## Letters

In October 2020, the following letters were sent or provided to relevant healthcare professionals:

- Esbriet (pirfenidone): important safety update and new recommendations to prevent drug-induced liver injury (DILI)
- Monofer 100mg/ml solution for injection/infusion▼ and Diafer 50mg/ml solution for injection▼: name change from iron isomaltoside to ferric derisomaltose
- Harvoni 45 mg/200 mg film-coated tablets (ledipasvir/sofosbuvir): supply of Irish product
- MUSE urethral sticks (alprostadil): Supply of packs with known anti-tamper seal issue
- Envarsus 1mg modified release oral tablets (tacrolimus): Interim Supply to Mitigate Supply Disruption
- Nytol Liquid Caramel Flavour 10mg/5ml oral solution Diphenhydramine Hydrochloride: removal of the allergy indication; should only be sold as an adult sleep aid*
- ONIVYDE pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion (Irinotecan): interim supply of Irish stock to mitigate supply disruption*
- Semglee▼ 100 units/ml x 3ml prefilled pens (Insulin glargine): interim supply of Portuguese stock to mitigate supply disruption*

*Letters first included in October 2020 Drug Safety Update

## Drug alerts

Class 2 Medicines Recall: Boots Dermacare 1% w/w Hydrocortisone Ointment (Batch 1DD), EL (20)A/47. Issued 6 October 2020. A specific batch of Hydrocortisone 1% w/w Ointment is being recalled as a precautionary measure due to retained samples showing presence of Pseudomonas aeruginosa. Stop supplying the batch immediately and return to supplier. Patients are advised to speak to their doctor or pharmacist if they experience any worsening of symptoms or other side-effects.

Class 2 Medicines Recall: Sanofi Epilim 500mg Gastro-Resistant Tablets EL (20)A/48. Issued 14 October 2020. Batches of this valproate medicine are being recalled as a precautionary measure due to out of specification results during routine stability testing. Stop supplying the batch immediately and return to supplier.

Class 3 Medicines Recall: Metoprolol 50 mg Tablets (PL 20075/0304), EL (20)A/49. Issued 14 October 2020. Upon decommissioning at the pharmacy and when scanning the serialised 2D code, the status of certain packs may report as 'EXPORT.' Although there is no risk to product quality, any remaining stock should be quarantined and returned.

Company led drug alert - Optiray® 300mg I/ml Solution for Injection or Infusion (PL 12308/0028) and Optiray® 350mg I/ml Solution for Injection or Infusion (PL 12308/0032). Issued 22 October 2020. Certain batches of these products are being recalled as a precautionary measure due to reports received from healthcare professionals on the difficulties in attaching the Luer lock adapter to the Luer tip of the pre-filled syringe and tubing catheter. In some cases this has resulted in leakages of contrast media during use.

Class 3 Medicines Recall: Theramex Ireland Ltd T/A Theramex HQ UK Ltd, AlfaD 0.25 microgram capsules (PL 49876/0001), EL (20) A/50. Issued 29 October 2020. Upon decommissioning at the pharmacy and when scanning the serialised 2D code, the status of packs may report as 'EXPORT'. This is a second alert for further batches identified. Although there is no risk to product quality, any remaining stock should be quarantined and returned.

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