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 advice for prescribers of tofacitinib for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Tofacitinib should not be used in patients aged older than 65 years, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives. This follows a finding of increased risks of major adverse cardiovascular events and malignancies compared with TNF-alpha inhibitors, which are also licensed for these conditions.

In our second article, we inform of new restrictions to the paediatric indication for chloral hydrate and cloral betaine to short-term treatment (maximum 2 weeks) of severe insomnia only when the child or adolescent has a suspected or definite neurodevelopmental disorder and when the insomnia is interfering with normal daily life. Chloral hydrate and cloral betaine should only be used when other therapies (behavioural and pharmacological) have failed. See advice on page 6.

On page 9, read about how you can support our sixth annual #MedSafetyWeek social media campaign, taking place on 1 to 7 November 2021. This year's theme is on the importance of reporting suspected adverse reactions to vaccines. Show your support by sharing MHRA material on social media, as well as discussing with colleagues and patients how reporting using the Yellow Card scheme helps to improve the safety of vaccines.

Following this article, read also about how you can attend a workshop on 21 October 2021 to support the setting up of the Yellow Card Biobank.

On page 12 we summarise recent advice relating to COVID-19 vaccines published since the September 2021 issue of Drug Safety Update. And on page 13 we include recent letters, recalls and notifications sent to healthcare professionals about medicines.

Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies

Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives.

Advice for healthcare professionals

Information on cardiovascular events

- a clinical safety trial in patients with rheumatoid arthritis aged 50 years or older with at least one cardiovascular risk factor (Study A3921133) found that the JAK inhibitor tofacitinib was associated with an increased risk of major adverse cardiovascular events compared with TNF-alpha inhibitors (etanercept or adalimumab)
- the following predictive risk factors were identified: age older than 65 years, current or past smoking, history of diabetes, and history of coronary artery disease (including past myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures)
- only consider use of tofacitinib in patients with these cardiovascular risk factors, irrespective of indication, if no suitable treatment alternative is available

Information on malignancy

- the same clinical safety trial in patients with at least one cardiovascular risk factor (some of which are also malignancy risk factors) found that tofacitinib was associated with an increased risk of malignancies (with the analysis excluding non-melanoma skin cancer [NMSC]), particularly lung cancer and lymphoma, compared with TNF-alpha inhibitors
- the following predictive risk factors were identified: age older than 65 years and current or past smoking
- only consider use of tofacitinib in patients with these and other malignancy risk factors (current or previous history of malignancy other than successfully treated NMSC), irrespective of indication, if no suitable alternative treatment is available

Advice for healthcare professionals to give to patients:

- tofacitinib treatment has been associated with an increased risk of heart attacks and certain cancers compared with another type of treatment (TNF-alpha inhibitors) – the incidence of these events is low and they have been linked to existing risk factors for these conditions such as older age or smoking
- patients who are already at increased risk of cardiovascular events or cancers should only be offered treatment with tofacitinib if their doctor feels there are no other suitable treatment options for their condition
- do not stop taking tofacitinib without first talking to your doctor
- always read the leaflet that accompanies your medicines and talk to your doctor, nurse, or pharmacist if you are concerned about any side effects

Safety review

Tofacitinib (Xeljanz▼) is a Janus kinase (JAK) inhibitor authorised for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (see Background section).

Study ORAL Surveillance (A3921133) was a large, randomised, active-controlled, clinical safety trial to evaluate the safety of tofacitinib versus tumour necrosis factor (TNF)-alpha inhibitors. The study involved 4,362 patients with rheumatoid arthritis aged 50 years or older and with at least one additional cardiovascular risk factor. In 2018, secondary findings of this study led to new measures to minimise risks of venous thromboembolism and serious and fatal infections with tofacitinib.

The co-primary endpoints of study A3921133 were adjudicated major adverse cardiac events and adjudicated malignancies (with the analysis excluding non-melanoma skin cancer).

Doses of tofacitinib included in the study were 5mg twice-daily and 10mg twice-daily and endpoints in these groups were compared with those from patients randomised to TNF-alpha inhibitors (etanercept, 50mg once a week subcutaneously, or adalimumab, 40mg once every other week subcutaneously).

In 2021, final results from study A3921133 showed tofacitinib to be associated with an increased incidence of non-fatal myocardial infarction and malignancies, particularly lung cancer and lymphoma.

These results prompted a review into these risks of tofacitinib and how they should be minimised. Prescribers of tofacitinib were informed of the final trial results in a letter in March 2021 with a further letter with the final recommendations sent in July 2021. The product information and educational materials for healthcare professional and patients will also be updated with this information.

Cardiocascular risk

Study A3921133 showed an increase in non-fatal myocardial infarction in patients treated with tofacitinib (hazard ratio (HR) for combined tofacitinib doses versus TNF-alpha inhibitors 2.20 (95% CI 1.02 to 4.75)). These calculations were based on events occurring on-treatment or within 60 days of treatment discontinuation. See letter from July 2021 for further data, including incidence rates.

Predictive factors for development of myocardial infarction (fatal and non-fatal) were identified using a multivariate Cox model with backward selection. These factors were age older than 65 years, male sex, current or past smoking, history of diabetes, and history of coronary artery disease (which includes past myocardial infarction, coronary heart disease, stable angina pectoris, or past coronary artery procedures).

Results suggest that these risks are associated with both the 5mg twice-daily dose and the 10mg twice-daily dose (which is approved only in ulcerative colitis).

Risk of malignancy

Study A3921133 showed an increase in malignancies (with the analysis excluding non-melanoma skin cancer), particularly lung cancer and lymphoma, in patients treated with tofacitinib compared with TNF-alpha inhibitors (HR for combined tofacitinib doses 1.48 (95% CI 1.04 to 2.09)). These calculations were based on events occurring on treatment or after treatment discontinuation up to the end of the study. See letter from July 2021 for further data, including incidence rates.

Predictive factors for development of malignancies (excluding non-melanoma skin cancer) were identified using a multivariate Cox model with backward selection. These were age older than 65 years and current or past smoking.

Lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post-marketing setting.[1,2,3,4]

Results suggest that these risks are associated with both the 5mg twice-daily dose and the 10mg twice-daily dose (which is approved only in ulcerative colitis).

Non-melanoma skin cancer has been previously reported in patients treated with tofacitinib and was listed in the product information before this review. The risk may be higher in patients treated with tofacitinib 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

1 Cohen SB and others. RMD open 2020: volume 6, number e001395.

2 van Vollenhoven RF and others. New England Journal of Medicine 2012: volume 367, pages 508-519.

3 van der Heijde D and others. Arthritis & Rheumatism 2013: volume 65, pages 559-570.

4 Fleischmann R and others. RMD Open 2017; volume 3, article e000491

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Background, including full indications for tofacitinib

Tofacitinib (Xeljanz▼) is a JAK inhibitor that was first authorised in the EU in March 2017. It is authorised for the treatment of:

- moderate to severe active rheumatoid arthritis in combination with methotrexate (unless not tolerated or inappropriate) in adults who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs (DMARD)
- active psoriatic arthritis in combination with methotrexate, in adults who have responded inadequately to, or who are intolerant of, one or more DMARD
- moderately to severely active ulcerative colitis in adults who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological agent

Tofacitinib is also indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA), in combination with methotrexate (unless not tolerated or inappropriate), in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs.

Approved formulations of tofacitinib are 5mg film-coated tablets, 10mg film-coated tablets and 11mg prolonged-release tablets. Tofacitinib 11 mg prolonged-release product once daily has demonstrated pharmacokinetic equivalence to tofacitinib 5 mg film-coated tablets twice-daily.

Based on previous findings from study A3921133, tofacitinib should be used with caution in patients with known risk factors for venous thromboembolism, regardless of indication and dosage. See March 2020, Drug Safety Update. In the same article, we also advised that patients older than 65 years of age are at an increased risk of serious infections and should be treated with tofacitinib only if there is no alternative treatment.

Report suspected adverse drug reactions

Tofacitinib (Xeljanz▼) is a black triangle medicine and any suspected adverse drug reactions (ADRs) should be reported 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 batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Report suspected side effects to medicines, vaccines or medical device and diagnostic adverse incidents used in coronavirus (COVID-19) using the dedicated Coronavirus Yellow Card reporting site or the Yellow Card app. See the MHRA website for the latest information on medicines and vaccines for COVID-19.

Article citation: Drug Safety Update volume 15, issue 3: October 2021: 1.

Chloral hydrate, cloral betaine (Welldorm): restriction of paediatric indication

The paediatric indication for chloral hydrate (for children aged 2 years and older) and cloral (previously chloral) betaine (children aged 12 years and older) has been restricted to short-term treatment (maximum 2 weeks) of severe insomnia only when the child or adolescent has a suspected or definite neurodevelopmental disorder and when the insomnia is interfering with normal daily life. Chloral hydrate and cloral betaine should only be used when other therapies (behavioural and pharmacological) have failed.

Advice for healthcare professionals:

- chloral hydrate and cloral betaine are indicated currently only for the short-term treatment of severe insomnia that is interfering with normal daily life and when other therapies (behavioural and pharmacological) have failed, as an adjunct to non-pharmacological therapies
- use of these medicines in children and adolescents is not generally recommended and should be under the supervision of a medical specialist
- following a national review of safety and efficacy data, the paediatric indication for chloral hydrate and cloral betaine has been further restricted to only children and adolescents with a suspected or definite neurodevelopmental disorder – this reflects current clinical practice
- for all patients, treatment should be for the shortest duration possible and should not exceed 2 weeks
- repeated courses are not recommended and can only be administered following medical specialist re-assessment
- following prolonged treatment, slowly taper the dose before discontinuation – abrupt discontinuation can lead to delirium
- report suspected adverse drug reactions associated with chloral hydrate and cloral betaine to the Yellow Card scheme

Advice to give to patients and carers:

- chloral hydrate and cloral betaine (brand names Welldorm Elixir and Welldorm) are short-term treatments (maximum of 2 weeks) for severe insomnia that is interfering with normal daily life when other therapies (behavioural and medicines) have not worked
- the MHRA and its independent advisors have reviewed the benefits and risks of these medicines in the paediatric population and recommended that they should only be used in children and adolescents who have a suspected or definite neurodevelopmental disorder
- always read the leaflet that accompanies your or your child’s medicines and talk to your doctor, nurse, or pharmacist if you have any concerns

Chloral hydrate and cloral betaine

Chloral hydrate (Welldorm Elixir) and its prodrug cloral betaine (Welldorm) are older drugs that retain some limited clinical usage. In 2009, following a national review of safety and efficacy, the authorisation for these medicines was restricted to severe insomnia that is interfering with normal daily life and where other therapies have failed, as an adjunct to non-pharmacological therapies (see Drug Safety Update, June 2009).

Chloral hydrate is licensed for use in adults and in children aged 2 years and older. Cloral betaine tablets are licensed for use in adults and adolescents aged 12 years and older.

National review of paediatric indication for chloral hydrate and cloral betaine

The MHRA has conducted a further review of safety and efficacy data for these medicines and sought independent expert advice from the Commission on Human Medicines (CHM), its Neurology, Pain and Psychiatry and Paediatric Medicines Expert Advisory Groups, as well as experts in paediatric sleep disorders.

No new safety concerns were identified. However, in view of known carcinogenicity data in animals and because of concerns regarding the lack of long-term studies, a risk in humans in long-term use cannot be excluded on the basis of available data. As such, the CHM recommended that the paediatric indication of all chloral hydrate and cloral betaine products should be restricted to use only in children and adolescents with suspected or definite neurodevelopmental disorders, where the benefits of short-term use outweigh any potential risk. These changes reflect current clinical practice.

The product information is being amended to further clarify that use of chloral hydrate and cloral betaine is not recommended in children and adolescents except in these very restricted circumstances and should only be under the supervision of a specialist.

Maximum duration of treatment and other precautions

Prolonged use of chloral hydrate and cloral betaine has been associated with tolerance and the risks of dependence and abuse. The maximum treatment period for these medicines in all patients has now been defined as 2 weeks in the product information.

Repeated courses are not recommended and can only be administered following medical specialist re-assessment. Following prolonged treatment, the dose should be slowly tapered before discontinuation to avoid delirium.

The Summaries of Product Characteristics and Patient Information Leaflets should be consulted for details of correct dose and other safety information – for example see chloral hydrate 500mg/5ml oral solution.

Off-label use for sedation in children

We are aware that chloral hydrate is used for sedation in children, for example in intensive care units and before diagnostic procedures. The immature metabolism of infants and neonates results in a prolonged half-life of metabolites in these groups, with an increased risk of undesirable effects. This factor and the lack of long-term studies to demonstrate safety should be taken into account when considering prescribing in this population outside the currently licensed indication.

Guidance should be consulted on prescribers' responsibilities when using a medicine off-label or using an unlicensed medicine.

Report suspected adverse drug reactions

Please continue to report suspected adverse drug reactions to the Yellow Card scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports 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)

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

Report suspected side effects to medicines, vaccines or medical device and diagnostic adverse incidents used in coronavirus (COVID-19) using the dedicated Coronavirus Yellow Card reporting site or the Yellow Card app. See the MHRA website for the latest information on medicines and vaccines for COVID-19.

Article citation: Drug Safety Update volume 15, issue 3: October 2021: 2.

MedSafetyWeek November 2021: support the safety of vaccines

Our sixth annual #MedSafetyWeek social media campaign will take place on 1 to 7 November 2021. This year's theme is on the importance of reporting suspected adverse reactions to vaccines.

Show your support by sharing MHRA material on social media, as well as discussing with colleagues and patients how reporting using the Yellow Card scheme helps to improve the safety of vaccines.

What healthcare professionals can do to support MedSafetyWeek – 1 to 7 November 2021:

- don't delay in reporting suspected adverse reactions to the Yellow Card scheme or via the Yellow Card app (download from the Apple App Store or Google Play Store)
- report suspected reactions to COVID-19 vaccines and medicines to the Coronavirus Yellow Card reporting site or Yellow Card app
- for each vaccine administered, accurately record in clinical health records details such as the vaccine and product name, batch number, expiry date, the dose, number of vaccinations (if multiple), and site of administration
- include the brand and batch number when reporting suspected adverse reactions to vaccines to the Yellow Card scheme
- for suspected reactions following a third or booster dose of a COVID-19 vaccine, please provide details of any suspected reactions following previous COVID-19 vaccinations, including which vaccine was previously received
- consider a discussion about common 'side effects' with your patient; you could talk about:
    - noting the batch number and reading the product information that comes with the vaccine – it lists possible reactions and advises them on what to do, including reporting side effects
    - the purpose of the Yellow Card scheme and the importance of reporting any suspected problems to help the safe use of vaccines for others
    - what to do if they do experience any suspected adverse reactions following vaccination
- talk to your colleagues about being vigilant for new or rare suspected reactions with vaccines or medicines and reporting them to the MHRA
- follow the MHRA on its social media channels and show your support by retweeting, commenting, liking, and sharing material with your social media contacts using #MHRAyellowcard, #MedSafetyWeek, #ReportSideEffects, and #patientsafety

About MedSafetyWeek

MedSafetyWeek is an annual MHRA social media campaign; now in its sixth year. The purpose of the campaign is to support awareness of reporting to the Yellow Card scheme. Each year, we use Drug Safety Update to ask healthcare professionals and organisations to begin preparations to support these important messages.

This #MedSafetyWeek, we call on all healthcare professionals, and especially those administering vaccines, national immunisation programme staff, vaccine recipients and their carers and families, and patient and healthcare professional organisations. Please report suspected adverse reactions following vaccination. We advise people not to wait for someone else to report their suspicions.

The annual #MedSafetyWeek forms part an international effort to raise awareness about the importance of reporting suspected adverse reactions by national medicines regulatory authorities from 65 countries across the globe and their stakeholders. It is led by Uppsala Monitoring Centre (UMC), a World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. The campaign is supported by members of the Heads of Medicines Agencies (HMA) and the International Coalition of Medicines Regulatory Authorities (ICMRA).

The #MedSafetyWeek 2021 project team consists of representatives from the following medicines regulators working collaboratively: the Medicines and Healthcare products Regulatory Agency (UK) as co-lead, International Society on Pharmacovigilance (ISoP) Egypt Chapter, the Health Products Regulatory Authority (Ireland), and the Food and Drugs Authority (Ghana).

Safety monitoring systems working effectively to protect public health

Vaccines are life-saving medicinal products that are given to protect individuals against serious infections and sometimes the most effective way to prevent infectious diseases.

Patient safety is number one priority for the MHRA. We rigorously monitor the safety of all UK-approved vaccines. Our experts routinely analyse Yellow Card data alongside all available safety data to determine which events and suspected reactions thought to be associated with a vaccine may be a potential signal and which may have occurred anyway in the absence of vaccination.

Reporting helps to identify new adverse reactions and gain more information about known effects. By completing a Yellow Card report, you can help the safe use of vaccines for everyone else.

Importance of brand and batch numbers in vaccine reports

As vaccines are usually complex biological products, it is important for traceability to record the brand and batch number when administering vaccines and include these details when completing a Yellow Card. If the brand name is unavailable, the active ingredient or antigen type should be clearly identified – for example the pneumococcal conjugate vaccine should be clearly distinguished from pneumococcal polysaccharide vaccine.

COVID-19 vaccines and Yellow Card reports

We continue to publish the summaries of Yellow Card report for the COVID-19 vaccines being used in the UK. The report, published weekly, summarises information received via the Yellow Card scheme and other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

We take every report of a suspected adverse reaction seriously and encourage everyone to report through the Coronavirus Yellow Card reporting site or using the Yellow Card app. There are also online resources available for you to use.

Resources for healthcare professionals

Information and resources for immunisation practitioners and other health professionals are available on the Public Health England collection on immunisation and the Green Book.

An e-learning training module on vaccine pharmacovigilance is also available via the WHO.

MHRA guidance on coronavirus (COVID-19) vaccines and vaccines safety is available on our website.

Yellow Card Biobank – Virtual Workshop

Another way healthcare professionals can help us is by attending our healthcare professional event on setting up a Yellow Card Biobank. The Yellow Card Biobank aims to research genetic factors behind adverse drug reactions and how we can use this data to reduce these incidents.

We ask practicing healthcare professionals to help shape this work. We are running a free 90 minute virtual event on Thursday 21 October 2021 and would appreciate hearing your thoughts. You can register for the event on Eventbrite. A certificate of attendance can be provided to those who require it.

Registration will close on Monday 18 October 2021 at 13:00.

Article citation: Drug Safety Update volume 15, issue 3: October 2021: 3.

COVID-19 vaccines: updates for October 2021

Recent information relating to COVID-19 vaccines and medicines that has been published since the September 2021 issue of Drug Safety Update, up to 1 October 2021.

Summaries of Yellow Card reporting and other recent MHRA publications

We continue to publish the summaries of the Yellow Card reporting for the COVID-19 vaccines being used in the UK. The report summarises information received via the Yellow Card scheme and will be published regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

We have also recently:

- published regulatory updates on the COVID-19 booster vaccine programme for winter 2021 to 2022
- updated the Summary of Product Characteristics and Sections 5 and 6 of the Patient Information Leaflet for COVID-19 Vaccine Janssen. For more information on COVID-19 Vaccine Janssen, see the Decision page
- approved the extension of the shelf life of the COVID-19 Vaccine Pfizer/BioNTech from the current 6 months to 9 months

We previously included summaries of latest COVID-19 information, including in the July 2021, August 2021 and September 2021 issues of Drug Safety Update.

See guidance on COVID-19 for all our latest information, including after publication of this article.

Reporting Yellow Cards

Suspected adverse reactions associated with COVID-19 vaccines should be reported to the MHRA through the MHRA's Coronavirus Yellow Card reporting site or via the Yellow Card app.

As these products are under additional monitoring this includes all suspected ADRs associated with these vaccines. This will allow quick identification of new safety information.

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

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected adverse events.

Article citation: Drug Safety Update volume 15, issue 3: October 2021: 4.

Letters and medicine recalls sent to healthcare professionals in September 2021

Letters

In September 2021, the following letters were sent or provided to relevant healthcare professionals:

- Bortezomib 2.5mg/ml Solution for Injection (Bortezomib): Interim Supply of over-labelled Italian stock to Mitigate Supply Disruption

Medicine Recalls and Notifications

In September 2021, recalls and notifications for medicines were issued on:

Class 4 Medicines Defect Information, Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets (EL (21)A/21). Issued 9 September 2021. Several batches of Rosuvastatin 5mg, 10mg, 20mg and 40mg film-coated tablets have been identified to include older versions of the Patient Information Leaflet in the product packs. The affected batches omit safety warnings on interactions and side effects – full details are available in the medicine notification. There is no risk to product quality as a result of this issue; however, healthcare professionals are advised to exercise caution when dispensing the product and provide an updated Patient Information Leaflet where possible.

Class 2 Medicines Recall: SANTEN Oy (trading as Santen UK Limited), IKERVIS 1 mg/mL eye drops, emulsion, EL (21)A/22. Issued 15 September 2021. Batches of Ikervis 1mg/ml eye drops (ciclosporin) are being recalled after particles or crystals of the active ingredient have been detected during stability testing. No reports of adverse events have been received by the Marketing Authorisation Holder, but there is potential for ocular irritation, eye pain or foreign body sensation due to the presence of particles. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 2 Medicines Recall: Accord-UK Ltd (Trading style: NorthStar), LEVOTHYROXINE TABLETS BP 50 micrograms EL (21)A/23. Issued 27 September 2021. A batch of levothyroxine 50 microgram tablets is being recalled due to variances in tablet hardness identified during stability testing. This is a precautionary recall, as tablets may crumble or break when removed from packaging. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Article citation: Drug Safety Update volume 15, issue 3: October 2021: 5.