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

Volume 14 Issue 10 May 2021

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.

NICE accredited
www.nice.org.uk/accreditation

MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

To subscribe to monthly email alerts of Drug Safety Update see: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/email-signup

In our issue this month, we issue advice for prescribers of levothyroxine for the control of hypothyroidism. Generic prescribing of levothyroxine remains appropriate for the majority of patients, but a small proportion of patients treated with levothyroxine have reported symptoms when their tablets were changed to a different product. We advise that if patients report symptoms when switching between different levothyroxine products, prescribers should consider testing thyroid function and if symptoms persist, they should consider consistently prescribing a specific product that is well tolerated by the patient.

On page 5, we include a summary of recent MHRA advice relating to COVID-19 vaccines up to 13 May 2021. And on page 6, we include recent letters, recalls and notifications sent to healthcare professionals about medicines and medical devices.

Levothyroxine: new prescribing advice for patients who experience symptoms on switching between different levothyroxine products

If a patient reports persistent symptoms when switching between different levothyroxine tablet formulations, consider consistently prescribing a specific product known to be well tolerated by the patient. If symptoms or poor control of thyroid function persist (despite adhering to a specific product), consider prescribing levothyroxine in an oral solution formulation.

Advice for healthcare professionals:

- generic prescribing of levothyroxine remains appropriate for the majority of patients and the licensing of these generic products is supported by bioequivalence testing
- a small proportion of patients treated with levothyroxine report symptoms, often consistent with thyroid dysfunction, when their levothyroxine tablets are changed to a different product – these cases are noted in UK professional guidelines
- if a patient reports symptoms after changing their levothyroxine product, consider testing thyroid function
- if a patient is persistently symptomatic after switching levothyroxine products, whether they are biochemically euthyroid or have evidence of abnormal thyroid function, consider consistently prescribing a specific levothyroxine product known to be well tolerated by the patient
- if symptoms or poor control of thyroid function persist despite adhering to a specific product, consider prescribing levothyroxine in an oral solution formulation
- report suspected adverse reactions to levothyroxine medicines, including symptoms after switching products, to the Yellow Card scheme

Background

Levothyroxine is authorised for the control of hypothyroidism. In the UK, prescribing of levothyroxine is usually generic, with no named product specified on the prescription. Patients may thus be changed between different levothyroxine products according to what is available at their local pharmacies, with the prescriber generally unaware of the specific product that the patient is taking at any particular time. This generic prescribing approach is supported by strict UK regulatory requirements for licensing to ensure compatibility (bioequivalence) between products.

Nevertheless, the MHRA receives reports of patients experiencing adverse events on switching between different levothyroxine products. The MHRA has conducted a review of the available data and sought advice from the Commission on Human Medicines as to whether any regulatory action is needed to minimise the risk of adverse events on switching between different levothyroxine products.

Reports considered by the review

Levothyroxine is one of the most commonly prescribed medicines in the UK. Between 1 January 2016 and 31 December 2020 there were a total of nearly 260 million packs of levothyroxine dispensed against a prescription in UK retail and hospital pharmacies.[1]

For the 5-year period between 1 January 2015 and 31 December 2019, the MHRA received 335 Yellow Cards reporting one or more of the terms ‘product substitution issue’, ‘condition aggravated’ or ‘drug ineffective’ with levothyroxine. The majority of reports were received from patients rather than healthcare professionals, with 47 of the cases having a healthcare professional reporter.

Associated symptoms were mostly consistent with hypothyroidism or hyperthyroidism, and included fatigue, headache, malaise, anxiety, palpitations, pruritus, nausea, myalgia, dizziness, arthralgia, feeling abnormal, alopecia, depression, abnormal weight gain, and insomnia.

Of the 335 cases, 12 reported a recurrence of their symptoms after a second trial with the medicine concerned. Only 27 of the 335 cases included reference to thyroid function test results. Of these, 9 suggested a hypothyroid state, with 4 hyperthyroid and 14 euthyroid. In most cases, thyroid function test data from before the product switch were not available to confirm that thyroid function was well controlled before the switch, or to indicate whether a substantial change in parameters within reference range had occurred.

The underlying causes for the symptoms experienced by patients switching between levothyroxine products are generally unclear.

Potential causative factors could include:

- gastrointestinal comorbidities potentially affecting levothyroxine absorption[2]
- concomitant use of medication reducing gastric acidity, which can also affect levothyroxine absorption[3]
- very low thyroid reserve[4]
- intolerance or allergy to an excipient in a particular brand
- specific genotypes relating to thyroid hormone synthesis or thyroid receptor function[5,6,7]

For the most part, the symptoms experienced on switching levothyroxine tablet formulations could indicate the need for dose adjustment. However, some patients experience symptoms despite thyroid function testing showing them as biochemically euthyroid.

These symptoms experienced by a minority of patients are acknowledged in UK professional guidelines. These guidelines note that although generic prescribing of levothyroxine is appropriate for the vast majority of patients, in rare cases a patient may require a specific levothyroxine brand to be prescribed.[7] In some patients, better control of thyroid function may be achieved with oral solution forms of levothyroxine than with tablets.[8,9,10]

Management of symptoms after product switching

CHM considered the reports in the UK and advised that levothyroxine should continue to be prescribed generically for most patients. If a patient reports symptoms after their brand of levothyroxine is changed, healthcare professionals are advised to consider testing of thyroid function and follow the 'Advice for healthcare professionals' section above.

The product information for levothyroxine tablets is being updated to include this advice for prescribers – see example Summary of Product Characteristics and Patient Information Leaflet.

Report on a Yellow Card

Please continue to report suspected adverse drug reactions 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 14, issue 10: May 2021: 1.

References

1. Hospital dispensing data covers usage of medicinal products within hospital pharmacies (irrespective of their source of supply). Data source: IQVIA MIDAS. Data derived by MHRA
2. McMillan M and others. Drugs in R&D 2016; 16, 53–68.
3. Yue CS and others. J Pharm Pharm Sci 2015; 18, 844–55.
4. Carswell JM and others. J Clin Endocrinol Metab 2013; 98, 610–17.
5. Al-Azzam IS and others. Hormones 2014; 13, 389–397.
6. Moran C and others. Thyroid 2017; 27, 973–982.
7. Okosieme O and others. Clinical Endocrinology 2015; 0, 1–10.
8. Negro R and others. Endocr Pract 2014; 20, 901–06.
9. Fallahi P and others. Laryngoscope Investig Otolaryngol 2018; 3, 405-408.
10. Virili C and others. Front Endocrinol 2018; 9, 10.

COVID-19 vaccines: updates for May 2021

A summary of advice recently issued by the MHRA relating to coronavirus (COVID-19), up to 13 May 2021.

Here we include a summary of key MHRA advice issued up to 13 May 2021 and since the publication of the April 2021 edition of Drug Safety Update.

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 take every report of a suspected adverse reaction seriously and encourage everyone to report through the Coronavirus Yellow Card reporting site.

We have also recently:

- published a statement following the Joint Committee on Vaccination and Immunisation's new advice on COVID-19 Vaccine AstraZeneca for people aged under 40

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

We previously included a summary of latest advice in the January 2021, February 2021, March 2021 and April 2021 issues of Drug Safety Update.

Article citation: Drug Safety Update volume 14, issue 10: May 2021: 2.

Letters and medicine recalls sent to healthcare professionals in April 2021

Letters

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

- EYLEA 40 mg/mL (aflibercept solution for intravitreal injection): Higher risk of intraocular pressure increase with the pre-filled syringe

- Colomycin (Colistimethate Sodium), 1 million IU, Powder for solution for injection, infusion or inhalation: replacement with Spanish Colomycin 1 million IU vials over-labelled with the UK label during supply shortage

Medicine Recalls and Notifications

Class 2 Medicines Recall: Ennogen Pharma Limited, Trimethoprim 200mg Tablets (PL 40147/0083), EL (21)A/10. A batch of Trimethoprim 200mg tablets is being recalled following complaints of a foreign tablet present in sealed containers. Following investigation, the foreign tablet was confirmed as Ennogen's 100mg Trimethoprim tablet. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Medical Device Safety Information

Recent MHRA Device Safety Information pages have been published on:

- Dexcom G6 Sensor: untested barrier methods to reduce skin reactions

- Total parenteral (TPN) and enteral nutrition bags manufactured by Diffuplast: Sterilisation issue

For all of the latest safety notices from the MHRA on drugs and medical devices, see Alerts and recalls for drugs and medical devices.

Article citation: Drug Safety Update volume 14, issue 10: May 2021: 3.