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HPRA DRUG SAFETY
NEWSLETTER

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In this Edition

Adverse reaction reporting during the COVID-19 pandemic – reminder

The HPRA wishes to remind healthcare professionals (HCPs) to continue to report any suspected adverse reactions to medicinal products to the HPRA. Additionally important at this time, the HPRA and European Medicines Agency (EMA) are requesting HCPs caring for patients with confirmed or suspected coronavirus disease (COVID-19) to report suspected adverse reactions to any of the medicinal products used in the treatment of these patients. This includes medicines administered to treat COVID-19, as well as those used in the management of long-term, pre-existing conditions. It also includes medicines that might be used off-label in the treatment of COVID-19. While there are currently no treatments authorised to treat COVID-19, HCPs will be aware that in the context of the pandemic, several treatments authorised for other medical conditions are being used in the treatment of COVID-19.

The HPRA greatly appreciates, and depends upon, the contribution of busy HCPs in continuing to report suspected adverse reactions, particularly at this time. The collection and evaluation of comprehensive reports is essential to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines.

Understanding of COVID-19 is still incomplete, including possible interactions with concomitant medications. By reporting suspected adverse reactions to medicines used in the context of COVID-19, patients and HCPs can help gather valuable evidence to inform decisions on the safe and effective use of medicines as the pandemic evolves and add to the body of knowledge currently being generated through clinical trials and other studies.

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When reporting suspected adverse reactions, *as much as possible* of the following information should be provided (however, please note that non-availability of all this information should not discourage report submission):

- Information on the **patient** who has experienced the adverse reaction, including age (or age group) and sex, and any additional available information such as weight/BMI, pregnancy status, co-morbidities etc.
- A description of the **suspected adverse reaction**, including clinical course, and outcome where known;
- The **name of the medicine** (brand name as well as active substance) suspected to have caused the adverse reaction;
- Dose and duration of treatment with the medicine;
- The **batch number** of the medicine administered (essential for reports involving biological medicines);
- Any concomitant medications (including non-prescription medicines, herbal remedies or contraceptives);
- For reports involving coronavirus infection, details on whether infection has been confirmed through testing or is based on clinical symptoms;
- **Reporter** (HCP or patient) details.

The full range of reporting options can be found at www.hpra.ie/report. **However, during the pandemic, wherever possible, HCPs, patients, and caregivers are asked to submit all reports of suspected adverse reactions electronically via the online reporting system only (accessible here), or by email to medsafety@hpra.ie.** This will enable us to process reports in a timely manner while working remotely. The HPRA has developed a dedicated section of our website to keep stakeholders informed of developments related to COVID-19 and the health products we regulate.

Picato▼ (ingenol mebutate) – EMA review concludes negative benefit-risk balance due to risk of skin malignancy

In September 2019 the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) commenced a review of data on skin cancer in patients using Picato (ingenol mebutate) to assess the impact of the available data on the benefit-risk balance of Picato. This review was triggered by data from some clinical studies that indicated a higher number of skin cancer cases, including cases of squamous cell carcinoma in patients using ingenol mebutate or a related investigational medicinal product containing ingenol disoxate. The initiation of, and background to, the review was previously highlighted in the HPRA's Drug Safety Newsletter (95th edition). During the course of the review, in January 2020, the EMA recommended an EU-wide suspension of Picato as a precautionary measure while the PRAC continued to review the available data regarding the possible risk of skin malignancy. A Direct Healthcare Professional Communication (DHPC) advising of the suspension was circulated by the marketing authorisation holder (MAH i.e. the company that holds the licence for a medicinal product), following approval by the HPRA, at that time. Healthcare professionals were advised to stop prescribing Picato and consider other treatment options, as appropriate. Batches of Picato were recalled from pharmacies and, in February 2020, the EU marketing authorisation was voluntarily withdrawn by the MAH.

The PRAC review has now concluded and considered that the risk of skin malignancy associated with Picato outweighs its potential benefits. The PRAC could not identify measures to minimise the risk of skin tumours in the treatment area to an acceptable level, and considered evidence that Picato's effectiveness is not maintained over time. In addition, it was noted that other treatment options are available for actinic keratosis. The marketing authorisation for Picato in the EU had already been withdrawn at the request of the MAH and the product will not return to the market in EU member states.

Background to the PRAC review

Picato (ingenol mebutate) is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. Picato was authorised for use throughout the European Union in 2012 as a 150 micrograms/gram gel (for use on the face and scalp) and 500 micrograms/gram gel (for use on the trunk and extremities).

In 2017, as a result of data from a double-blind, vehicle-controlled study in patients with actinic keratosis on trunk and extremities (study LP0105-1020), the product information for Picato was updated to reflect the potential for development of benign skin tumours (keratoacanthoma) in those treated with ingenol mebutate. In addition, an increased incidence of squamous cell carcinoma in those treated with ingenol mebutate compared to imiquimod has been observed in the results of the now finalised long-term safety study LP0041-63 (3.3% versus 0.4% of patients). A meta-analysis of four studies of ingenol disoxate (an ester related to ingenol mebutate) found an increased incidence of skin tumours at 14 months in those treated with ingenol disoxate compared to those treated with vehicle. An imbalance in tumour incidence was noted for a number of tumour types including basal cell carcinoma, Bowen's disease and squamous cell carcinoma. Post-marketing reports of skin tumours in Picato-treated patients have also been received. Time to onset ranged from weeks to months.

Advice to Healthcare Professionals

- The risk-benefit balance of Picato (ingenol mebutate) is negative due to the risk of skin malignancy. Picato is no longer authorised in the EU.
- Stop prescribing Picato and consider other treatment options as appropriate.
- Continue to advise patients to be vigilant for any skin lesions developing within the treatment area and to seek medical advice immediately should any occur.
- Batches of Picato have been recalled from pharmacies.

Key messages

The risk-benefit balance of Picato (ingenol mebutate) is negative due to the risk of skin malignancy. Picato is no longer authorised in the EU.

Healthcare professionals should stop prescribing Picato and consider other treatment options as appropriate.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

* *Further details on Picato (ingenol mebutate) are available at www.hpra.ie and www.ema.europa.eu.*

Levetiracetam – risk of abnormal and aggressive behaviours

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has completed a periodic review of the available safety data in association with the pyrrolidone derivative, levetiracetam*.

Levetiracetam is indicated in the treatment of specified forms of epilepsy, either as a monotherapy or as adjunctive treatment in defined circumstances. Abnormal behaviour (including irritable and aggressive behaviours) is already considered an important identified risk for levetiracetam, and this information is reflected in the approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)), where several adverse reactions relating to this risk, including hostility/aggression, nervousness/irritability, psychotic disorder, abnormal behaviour, anger, affect lability/mood swings and agitation are described, as are depression, anxiety, suicidal ideation/attempt and completed suicide. Based on the review of data on safety and efficacy, the PRAC considered that the warnings in the product information should be updated to include a warning on the risk of abnormal and aggressive behaviours in patients treated with levetiracetam.

Advice to Healthcare Professionals

- Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness.
- Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered.
- Healthcare professionals should counsel patients/carers to tell their doctor/pharmacist if any of the following side effects become serious or last longer than a few days: Abnormal thoughts, feeling irritable or reacting more aggressively than usually or if patients or their family/friends notice important changes in mood or behaviour.
- If levetiracetam is to be discontinued, gradual withdrawal is recommended. Healthcare professionals should refer to section 4.2 of the Summary of Product Characteristics (SmPC).

Key messages

Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness and these are described in the currently-approved product information.

The product information (SmPC) and Package Leaflet (PL) for levetiracetam products will be amended to include a warning reflecting the current understanding of the risk of abnormal and aggressive behaviours in patients treated with levetiracetam.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

* *Products currently authorised include Keppra, Matever and Levetiracetam. Further details are available at www.hpra.ie and www.ema.europa.eu.*

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Cyproterone acetate – restrictions in use due to risk of meningioma

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently completed a review of the available data on the risk of meningioma associated with cyproterone acetate* (CPA). This review considered data from epidemiological studies, post-marketing case reports and data submitted by the relevant marketing authorisation holders (MAH's, i.e. the companies that hold the licences for CPA-containing medicines).

The PRAC concluded from their review of the data that, while the absolute risk of meningioma in association with CPA use remains low, the risk increases with increasing cumulative doses. The PRAC noted that most cases occur after prolonged exposure to high doses of CPA, but cases of meningioma have also been identified after short-term exposure to high doses. The PRAC therefore recommended that in all indications except prostate carcinoma, treatment with daily doses of ≥10mg of CPA should be restricted to situations where alternative treatments or interventions are unavailable or are considered inappropriate, and that the lowest possible effective dose should be used.

While the PRAC noted that the available data do not indicate an increased risk of meningioma in association with low-dose combination products containing 2 mg or less of CPA, the PRAC recommended that low dose combination products should also be contraindicated in patients with meningioma or a history of meningioma.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for CPA-containing medicines will be updated to reflect current knowledge on the risk of meningioma associated with treatment. A Direct Healthcare Professional Communication (DHPC) was prepared by the MAH in April 2020 advising healthcare professionals of the outcome of the PRAC review and is available from the HPRA website (www.hpra.ie).

Background to the PRAC review

CPA is a synthetic progesterone derivative with anti-androgenic properties. It is authorised at a strength of 100 mg for use in men for antiandrogen treatment in inoperable carcinoma of the prostate, and for reduction of drive in sexual deviations. CPA is also authorised at a strength of 2 mg in combination with ethinylestradiol for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age. For this indication, CPA in combination with ethinylestradiol should only be used after topical therapy or systemic antibiotic treatments have failed and should not be used in combination with other hormonal contraceptives.

The association of high dose (50 mg/day) CPA with meningioma was first described in 2008[1] and the Summary of Product Characteristics (SmPC) of CPA-containing medicines with a strength of ≥ 10 mg was updated at that time. The update included a contraindication in patients with meningioma or a history of meningioma, in addition to a warning regarding the risk of meningioma associated with long-term use of CPA at doses of 25 mg/day and above. A recently conducted epidemiological cohort study based on data from the French National Health Data System (SNDS), included a population of 253,777 women using 50 or 100 mg CPA[2]. The incidence of meningioma requiring surgery or radiotherapy was compared between women who had received a cumulative dose of ≥ 3 g and women who had received a cumulative dose of < 3 g. The results of the study demonstrated that there is a cumulative dose-dependent association between CPA and meningioma.

Advice to Healthcare Professionals

- The occurrence of meningiomas (single and multiple) has been reported in association with the use of CPA, primarily at doses of 25 mg/day and above.
- The risk of meningioma increases with increasing cumulative dose.
- Use of CPA is contraindicated in patients with a meningioma or a history of meningioma.
- Patients should be monitored for meningiomas in accordance with clinical practice.
- If a patient treated with CPA is diagnosed with meningioma, treatment must be stopped permanently.
- For reduction of drive in sexual deviations in men, CPA 100 mg can be used when other interventions are considered inappropriate.
- The use of CPA for the treatment of inoperable prostate cancer remains unchanged.
- The product information for CPA-containing medicines will be updated to reflect current knowledge on the risk of meningioma associated with treatment.
- A Direct Healthcare Professional Communication (DHPC) advising healthcare professionals of the outcome of the PRAC review is available from the HPRA website (www.hpra.ie).

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Key messages

Use of CPA is contraindicated in patients with a meningioma or a history of meningioma.

Patients should be monitored for meningioma in accordance with clinical practice and if a patient treated with CPA is diagnosed with meningioma, treatment must be stopped permanently.

For reduction of drive in sexual deviations in men, CPA 100 mg can be used when other interventions are considered inappropriate.

The use of CPA for the treatment of inoperable prostate cancer remains unchanged.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

** Cyproterone acetate-containing products include Androcur and Dianette. Further details are available at www.hpra.ie.*

References

1. *Froelich S, Dali-Youcef N, Boyer P, et al. Does cyproterone acetate promote multiple meningiomas? Endocrine Abstracts. 2008; 16: P158*
2. *Weill A et al. (2019 Jun). Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme. Paris: ANSM. https://www.ansm.sante.fr/var/ansm_site/storage/original/application/b632fbd0387cd9e80a8312469ed52d2a.pdf*

Carbimazole and propylthiouracil – use in pregnancy and in women of childbearing potential

Carbimazole

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of information on the known risk of congenital malformations associated with carbimazole exposure during pregnancy. Carbimazole is used in the management of hyperthyroidism, in preparation for thyroidectomy in hyperthyroidism, and prior to and post radio-iodine treatment. Carbimazole is a pro-drug and undergoes rapid metabolism to the active metabolite thiamazole. Data from epidemiological studies and case reports strengthens the evidence that carbimazole/thiamazole exposure during pregnancy is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses. Reported malformations include aplasia cutis congenita, craniofacial malformations, defects of the abdominal wall and gastrointestinal tract, and ventricular septal defects.

Advice to healthcare professionals

- Women of childbearing potential should use effective contraception during treatment with carbimazole.
- The use of carbimazole during pregnancy should be reserved for cases where a definitive therapy of the underlying disease (thyroidectomy or radio-iodine treatment) was not suitable prior to pregnancy, or in cases of new occurrence/recurrence during pregnancy.
- Carbimazole must only be used during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones.
- If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.
- A Direct Healthcare Professional Communication (DHPC) to communicate the strengthened advice on contraception was circulated by the Marketing Authorisation Holders for carbimazole-containing products (following approval by the HPRA) to relevant healthcare professionals and is available from the HPRA website.

Propylthiouracil

The PRAC undertook a separate review of the risk of congenital malformations associated with propylthiouracil exposure during pregnancy. Propylthiouracil is indicated for the treatment of hyperthyroidism. The available evidence from epidemiological studies is conflicting regarding the risk of congenital malformations associated with the use of propylthiouracil during pregnancy. Individual benefit/risk assessment is necessary before treatment with propylthiouracil during pregnancy. Propylthiouracil should be administered during pregnancy at the lowest effective dose without additional administration of thyroid hormones, and close maternal, foetal and neonatal monitoring is recommended.

Key messages

Data from epidemiological studies and case reports strengthen the evidence that carbimazole/thiamazole is associated with an increased risk of congenital malformations especially when administered in the first trimester and at high doses. It is therefore recommended that women of childbearing potential should use effective contraception during treatment with carbimazole.

Carbimazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

Epidemiological data are conflicting regarding the risk of congenital malformations associated with the use of propylthiouracil during pregnancy. Individual benefit/risk assessment should be undertaken. The lowest effective dose of propylthiouracil without additional administration of thyroid hormones should be used, and close maternal, foetal and neonatal monitoring is recommended.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these medicines has been updated to reflect this information.

Any reports of suspected congenital malformations should be submitted to the HPRA via the available options (www.hpra.ie/report).

Carbimazole – risk of acute pancreatitis

Post-marketing reports of acute pancreatitis in association with the use of medicinal products containing carbimazole/thiamazole have been received across the EU. Although the mechanism is not fully understood, decreased time to onset after re-exposure could suggest an immunological mechanism.

Immediate discontinuation is required in patients who develop pancreatitis following exposure to carbimazole and treatment should not be restarted. Affected patients should be switched to alternative treatment following an individual benefit/risk assessment.

A Direct Healthcare Professional Communication highlighting this risk (DHPC) (see above) was circulated to relevant healthcare professionals, and published on the HPRA website. The product information (SmPC and PL) for carbimazole-containing products has been updated to reflect this information.

Key messages

Acute pancreatitis has been reported following treatment with carbimazole/thiamazole.

Treatment should be discontinued immediately if pancreatitis occurs following exposure to carbimazole and re-exposure must be avoided as it could result in recurrence of potentially life-threatening acute pancreatitis with decreased time to onset.

Any reports of suspected pancreatitis associated with use of carbimazole should be submitted to the HPRA via the usual methods (www.hpra.ie/report).

** Products currently authorised in Ireland include Neomercazole and Carbimazole. Further details are available at www.hpra.ie*

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Testosterone-containing medicinal products: caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE)

Following a recent periodic review of oral, topical, and injectable testosterone-containing medicinal products*, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended an update to the product information for testosterone-containing medicinal products. These products are licensed in Ireland as testosterone replacement therapy for male hypogonadism. Based on a review of the literature, and in particular data from studies by Glueck et al.[1,2], the PRAC considered that the existing warning in the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) regarding clotting disorders should be amended to highlight the need for caution in patients with risk factors for venous thromboembolism (VTE). Similarly, a warning will be included to indicate that in patients with thrombophilia, cases of VTE have been reported, including some in those on anticoagulant treatment. Therefore, continuing testosterone treatment after a first thrombotic event in patients with thrombophilia should be carefully evaluated, and in the case of treatment continuation, further measures should be taken to minimise the individual VTE risk. Moreover, the PRAC considered it pertinent to specify risk factors for VTE in the Package Leaflet and additionally to include signs and symptoms of thrombosis in order to highlight these for patients.

Advice to Healthcare Professionals

- Topical, oral and injectable testosterone-containing medicinal products should be used with caution in patients with risk factors for venous thromboembolism (VTE).
- In patients with thrombophilia, cases of VTE have been reported, including some in those on anticoagulant treatment. Continuing testosterone treatment in patients with thrombophilia requires careful evaluation after a first thrombotic event and implementation of measures to minimise the individual VTE risk.

Key messages

Topical, oral and injectable testosterone-containing medicinal products should be used with caution in patients with risk factors for venous thromboembolism (VTE).

In patients with thrombophilia, cases of VTE have been reported, including some in those on anticoagulant treatment, and continuing testosterone treatment in such patients requires careful evaluation after a first thrombotic event.

The product information for testosterone-containing medicinal products are being updated to reflect the outcome of the PRAC review.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

* *Testosterone-containing medicines licensed in Ireland include Androgel, Nebido, Restandol Testocaps, Testarzon, Testim, Testogel, and Tostran. Further details on testosterone-containing medicines are available at www.hpra.ie and www.ema.europa.eu.*

References

1. *Glueck CJ, Goldenberg N, Wang P. Thromboembolism peaking 3 months after starting testosterone therapy: testosterone–thrombophilia interactions. J Investig Med. 2017; 0:1-6.*
2. *Glueck CJ, Goldenberg N, Wang P. Testosterone Therapy, Thrombophilia, Venous Thromboembolism, and Thrombotic Events. J Clin Med. 2018;8(1).*

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Hydroxychloroquine (Plaquenil 200mg tablets)	Important Safety Information from Sanofi Ireland on Hydroxychloroquine (Plaquenil 200mg Film-Coated Tablets PA540/155/1): Risk of QT prolongation in the context of COVID 19
Flucytosine	Updated recommendations for the use in patients with dihydropyrimidine dehydrogenase (DPD) deficiency

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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