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Rivaroxaban (Xarelto) – Increase in all-cause mortality, thromboembolic and bleeding events in patients after transcatheter aortic valve replacement in a prematurely stopped clinical trial

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee ([PRAC](#)) was informed of an increase in all-cause mortality, thromboembolic and bleeding events in patients treated with rivaroxaban after transcatheter aortic valve replacement (TAVR) reported in a phase III clinical study (GALILEO) which was prematurely stopped. Data collection on included subjects is ongoing ahead of closure of the trial database with further analyses to be undertaken once complete, therefore, the final results of the study are still pending.

The GALILEO study is a randomised, open label, active-controlled, multicentre phase III trial to evaluate clinical outcomes after a successful TAVR in patients randomised to either a rivaroxaban-based anticoagulation strategy (rivaroxaban 10mg once daily and acetylsalicylic acid (ASA) 75-100mg once daily, for 90 days followed by maintenance with rivaroxaban 10mg once daily) or an antiplatelet-based strategy (clopidogrel 75mg and ASA 75-100mg once daily for 90 days followed by maintenance with ASA). Patients with

atrial fibrillation at randomisation were excluded from the trial.

In August 2018, the independent Data Safety Monitoring Board (DSMB) responsible for trial oversight recommended stopping the trial as a preliminary analysis of available data suggested an imbalance between the study groups in all-cause mortality, thromboembolic and bleeding events. The incidences in the rivaroxaban group (n = 826) and the antiplatelet group (n = 818), respectively, were 11.4% versus 8.8% for death or first thromboembolic events, 6.8% versus 3.3% for all-cause death and 4.2% versus 2.4% for primary bleeding events. These results are preliminary and based on incomplete data collection. The PRAC will evaluate the final study data when they are available and will assess any impact on the authorised indications of Xarelto.

A Direct Healthcare Professional Communication ([DHPC](#)) has been distributed by the Marketing Authorisation Holder (following HPRA approval) to relevant healthcare professionals.

Advice to Healthcare Professionals

- Rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients following TAVR, and should not be used in these patients. It should only be used for the currently approved indications as listed in the approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)).

Key Message

A phase III clinical trial in patients after TAVR has been terminated early based on preliminary results showing an increase in all-cause mortality, thromboembolic and bleeding events in patients randomised to a rivaroxaban-based anticoagulation strategy compared with those randomised to an antiplatelet-based strategy.

Rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR and should not be used in these patients.

Rivaroxaban is subject to additional monitoring requirements and any suspected adverse reactions should be reported to the HPRA via the usual methods (www.hpra.ie).

Further details available on www.hpra.ie and www.ema.europa.eu

Insulin-containing products – Risk of medication errors associated with extraction of insulin from pre-filled pens and cartridges for reusable pens

Extracting insulin from cartridges for reusable pens and pre-filled (disposable) pens should never occur as it poses a risk of medication error due to:

- Mix-up of insulin types,
- Dose conversion errors, especially with different insulin strengths,
- Damage to pen/cartridge accuracy.

Medication errors leading to a risk of serious hyper and/or hypoglycaemic episodes (dysglycaemia) are a recognised potential risk with all insulin containing products. Following approval of high-strength insulins in the EU, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) highlighted concerns about the potential for medication error and the risk of significant over or under dosing, including errors associated with extraction from pre-filled pens, which led to the development of European Medicines Agency (EMA) [guidance](#) on risk minimisation for high strength and fixed combination insulin products in November 2015. Following concerns raised about the risk of severe harm due to withdrawal of insulin from pen devices, an EU wide review of the issue was undertaken, resulting in the following recommendations.

If a pre-filled pen or a reusable pen fails or malfunctions then patients should be advised of the following actions:

- Always have replacement pre-filled pens, needles and/or cartridges for reusable pens available,

- Try a replacement needle and/or a new cartridge for reusable pens. If the replacement fails then use a replacement pen.

Patients who inject insulin-containing products from pre-filled pens and cartridges for reusable pens should be advised of the following:

- How to obtain a replacement pen in an emergency
 - For pre-filled pens, to always have a spare pen available,
 - For reusable pens, to contact their prescribing doctor to discuss alternative products.
- When more frequent blood glucose monitoring may be required
- When to seek medical assistance
- Tampering with a pre-filled pen or with a cartridge for a reusable pen can lead to inaccuracies in the administration of future doses and should be avoided.

Insulin pens (both pre-filled pens and re-useable pens) and cartridges for reusable pens are for **single patient use only**. Blood and biological matter can regurgitate into the insulin cartridge during injection. Re-using a cartridge or pen for another patient exposes the second patient to a risk of transmission of any blood borne pathogens (for example hepatitis B virus), with which the initial patient may be infected.

Key Message

Extracting insulin from cartridges and pre-filled pens via syringe is not recommended and can result in insulin mix ups and dose conversion errors, some of which can be life threatening.

Patients should be:

- advised on what actions to take in case of pen failure,
- aware of how to obtain a replacement pen in case of emergency,
- aware when more frequent blood glucose monitoring may be necessary and
- advised on when to seek medical assistance.

The approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for the medicines in question will be updated, where necessary, with this information.

Two letters highlighting this information (one for [healthcare professionals](#) and one for [patients](#)) have been circulated by the Marketing Authorisation Holders (MAH i.e. license holder for a medicine) to relevant healthcare professionals and are available from the HPRa website.

Any suspected adverse reactions arising from medication errors associated with insulin-containing products should be reported to the HPRa via the usual methods (www.hpra.ie).

Insulin-containing products include Apidra, Insuman Basal, Insuman Comb, Insuman Rapid, Lantus, Insulatard, Levemir, NovoMix 30, NovoRapid, Tresiba, Fiasp, Abasaglar, Humalog & Humulin. Further details available on www.hpra.ie and www.ema.europa.eu

Hydrochlorothiazide (HCTZ) – Risk of non-melanoma skin cancer (NMSC)

Two recent population-based observational studies, conducted in Denmark, have shown a cumulative dose-response association between hydrochlorothiazide (HCTZ) and non-melanoma skin cancer (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)).

One study [1] included 71,533 cases of basal cell carcinoma (BCC) and 8,629 cases of squamous cell carcinoma (SCC) matched to 1,430,833 and 172,462 population controls, respectively. A cumulative dose of HCTZ of $\geq 50,000$ mg was associated with an adjusted odds ratio (OR) of 1.29 (95% confidence interval (CI): 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A 50,000 mg cumulative dose corresponds to 12.5 mg HCTZ taken daily for about 11 years.

In another study [2] 633 cases of lip-cancer (SCC) were matched with 63,067 population controls. A cumulative dose-response relationship was observed, with adjusted OR 2.1 (95% CI: 1.7-2.6) for ever users, increasing to OR 3.9 (3.0-4.9) for a cumulative dose of HCTZ of $\sim 25,000$ mg) and to OR 7.7 (5.7-10.5) for the highest cumulative dose of HCTZ ($\sim 100,000$ mg).

Although these studies have some limitations, a possible mechanism for the observations is the known photosensitising action of hydrochlorothiazide.

Incidence rates of NMSC are dependent on skin phenotypes and other factors, and vary across Europe. The incidence rate of SCC is estimated to be 1 to 34 cases per 100,000 inhabitants per year and the incidence rate of BCC is estimated to be 30 to 150 cases per 100,000 inhabitants per year.

Depending on the cumulative dose of HCTZ, based on the results of the two Danish epidemiological studies, the risk of SCC may be increased by approximately 4 to 7.7-fold and the risk of BCC by 1.3-fold.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has assessed the available data and highlighted the following recommendations, based on the currently available information:

Advice to Healthcare Professionals

- Patients taking HCTZ alone or in combination with other products should be informed of the risk of non-melanoma skin cancer and should be advised to regularly check their skin for any new lesions as well as changes to existing ones.
- Patients should be advised to discuss any suspicious skin lesions promptly with an appropriate healthcare professional.
- Suspicious skin lesions should be examined promptly, and histological examinations of biopsies may be warranted.
- In line with routine best practise, patients should be advised to limit exposure to sunlight and UV rays to minimise the risk of skin cancer. This should include seeking shade and avoiding artificial tanning. Patients should also be advised to use adequate sun protection when exposed to sunlight and UV rays (for example by using a high factor sunscreen, sunglasses, hats, and protective clothing)
- The use of HCTZ in patients who have previously been diagnosed with skin cancer should be carefully considered.

Key Message

An increased risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) in patients with exposure to increasing cumulative doses of HCTZ has been observed in epidemiological studies conducted in Denmark.

Patients should be informed of these risks and advised about limiting exposure to sunlight and UV rays and using adequate sun protection, as well as being vigilant for new or changing skin lesions.

Suspicious skin lesions should be examined promptly.

Use of HCTZ should be considered carefully in patients with a previous history of skin cancer.

The approved product information will be updated with this information shortly.

Any suspected adverse reactions should be reported to the HPRA via the usual methods (www.hpra.ie).

Further details on HCTZ-containing products available on www.hpra.ie and www.ema.europa.eu

References

- [1] Pedersen SA, Gaist D, Schmidt SAJ et al. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. *J Am Acad Dermatol* 2018;78(4):673-681
- [2] Pottegard A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; 282(4): 322–331.

Dolutegravir – Neural tube defects reported in infants born to women exposed at the time of conception

The European Medicine Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed its precautionary advice issued in May 2018 following initiation of an EU-wide review on the use of dolutegravir in pregnant women and women of child bearing potential. The review commenced following preliminary results from an ongoing observational study (Tsepamo study) in Botswana which suggested an increased incidence of neural tube defects in infants born to women who became pregnant while taking dolutegravir.

Preliminary data from the surveillance study suggested an increased incidence of neural tube defects (0.9%) in mothers exposed to dolutegravir at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%).

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%). As

neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of malformative and foeto/neonatal negative effects. However, as the mechanism by which dolutegravir may interfere in human pregnancy is unknown, safety in use during the second and third trimester cannot be confirmed. Dolutegravir should only be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.

As the study is still on-going, a further assessment will be carried out when the final results become available (expected in 2019). In the meantime the following measures are recommended:

Advice to Healthcare Professionals

- Women of child bearing potential should undergo pregnancy testing before initiation with dolutegravir.
- Women of child bearing potential who are taking dolutegravir should use effective contraception throughout treatment.
- Due to the potential risk of neural tube defects, dolutegravir should not be used during the first trimester unless there is no alternative.
- Dolutegravir should only be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.
- A Direct Healthcare Professional Communication (DHPC) was circulated by the Marketing Authorisation Holder (i.e. the pharmaceutical company who holds the license for the medicines in question), following approval by the HPRA, to relevant healthcare professionals in May 2018. The Health Protection Surveillance Centre (HPSC) has also updated its [guidance](#) on post-exposure prophylaxis to reflect the current recommendations.

Key Message

Preliminary results from one study has shown an increase in neural tube defects in babies born to mothers who took dolutegravir at the time of conception.

Pending the final study results, certain measures are recommended including:

- Women of childbearing potential should undergo pregnancy testing before treatment with dolutegravir is initiated.
- Advise women of child bearing potential to use effective contraception throughout treatment.
- Dolutegravir should not be used during the first trimester due to the potential risk of neural tube defects and should only be used in second and third trimesters if the expected benefit outweighs the potential risks to the foetus.
- Dolutegravir is subject to additional monitoring requirements and any suspected adverse reactions should be reported to the HPRA via the usual methods (www.hpra.ie).

Further details on dolutegravir-containing products (Tivicay, Triumeq, Juluca) are available on www.hpra.ie

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

| PRODUCT | SAFETY ISSUE |
|---|---|
| Fluoroquinolones (systemic and inhaled) | Risk of aortic aneurysm and dissection |
| Hydrochlorothiazide | Risk of non-melanoma skin cancer |
| Xarelto (rivaroxaban) | Increase in all-cause mortality, thromboembolic and bleeding events in patients after TAVR |
| Insulin The DHPC for healthcare professionals The DHPC for patients | Risk of medication errors associated with extraction of insulin from cartridges and pre-filled pens |
| Keppra (levetiracetam) | Updated data on use in pregnancy |
| Hydroxyethylstarch Solutions | New measures to reinforce existing restrictions due to increased risk of renal dysfunction and mortality in critically ill or septic patients |

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.