10 April 2014
EMA/PRAC/195699/2014 - ADOPTED
Pharmacovigilance Risk Assessment Committee

PRAC recommendation

Clindamycin – drug interaction with warfarin leading to International Normalised Ratio (INR) increased

This is a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

1. Administrative details

Substance (invented name)	Clindamycin
Authorisation procedure	Non-centralised
Signal (EPITT No)	Drug interaction (MedDRA PT) International Normalised Ratio (INR) increased (MedDRA PT) EPITT Ref. 17700
PRAC meeting date	7 – 10 April 2014
Signal identifier	United Kingdom
PRAC rapporteur(s)	Julie Williams (UK)
Name of product team leader	N/A
Name of scientific administrator	Cosimo Zaccaria
Status	Signal follow-up
Date of adoption	10 April 2014

2. Prioritisation and recommendation

Evidence evaluated and prioritisation/public health importance

The MAH has performed a comprehensive search of the Pfizer safety database through to 10th December 2013 for all cases reporting clindamycin as the suspect drug with the anti-coagulants acenocoumarol, fluindione, phenprocoumon, warfarin, warfarin potassium, warfarin sodium, warfarin

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

sodium clarhrate, anisindione, clorindione, coumetarol, dicoumarol, diphenadione, ethyl biscoumacetate, ethylidendicoumarol, fepromaron, phenindione, tioclomarol, vitamin K antagonists, or wobenzym as co-suspected or concomitant drugs.

Based on the information reviewed, the MAH considers that the data do not represent sufficient evidence to conclude that there is a risk of an interaction, whereby clindamycin potentiates the anticoagulant effect of warfarin or other oral anticoagulants.

This search retrieved 49 cases, two of which were from clinical studies, three from literature sources and forty four were spontaneously reported. Eight of these cases did not report other co-suspect and/or concomitant medicines.

Lincomycin was included in the search for completeness (cut-off date 02 January 2014). This literature search revealed two additional cases mentioning increased INR when both clindamycin and warfarin were administered.

Twenty three cases specifically report drug interaction and there are two cases of positive dechallenge. This event may be under-reported by HCPs due to the known instability of INR, the familiarity of warfarin related haemorrhages, and alternative potential causal factors.

A retrospective study of 23 paediatric patients (Johnson et al) who received 89 courses of antibiotics reported a mean increase of INR of 2.0 in cases where patients were administered clindamycin.

The mean INR increase found was relatively modest at 0.9 (from 2.7 to 3.6 only) across all antibiotics; however, this did move the mean INR out of the target range of 2.5 – 3.5. Although 89 courses of antibiotics were administered, due to the likely mechanisms of this interaction (i.e. disruption of synthesis/absorption of vitamin K from the gut flora) individual patients are likely to be more susceptible than others. The greatest changes in INR occurred between days 3 and 7 following antibiotic administration; this is similar to that seen in spontaneous cases. The mean INR increase found with clindamycin (n=3) of 2.0 is greater than that found with other antibiotics in the study (amoxicillin:0.8 (n=20), minocycline:0.7 (n=3), co-amoxiclav:0.8 (n=3), azithromycin:0.6 (m=11), clarithromycin:1.0 (n=5) and similar to that of erythromycin:2.3 (n=2)) which currently contain warnings regarding the monitoring of INR with concomitant administration of warfarin/coumarin based anticoagulants, it is also significantly higher than the mean INR increase of 0.9 reported for antibiotics as a whole. It is noted that this is a small study with several limitations, not least that it has been shown that younger patients are more susceptible to alterations in INR and generally require more frequent adjustments of warfarin dose.

A pharmacokinetic interaction between clindamycin and the R enantiomer of warfarin is considered possible based on the metabolic pathways of these drugs however it is noted that this is unlikely to be solely responsible for the increases in INR observed in the case reports. Published literature hypothesizes that treatment with broad spectrum antibiotics may alter the gut flora and therefore both synthesis and absorption of vitamin K. Clindamycin is typically considered a narrow spectrum antibiotic however it is still likely to have effects on the gut flora that could plausibly affect synthesis and absorption of vitamin K. It is noted that Baillargeon et al considered only patients who were hospitalised with a primary diagnosis of bleeding. The study concluded that further studies could elucidate the causal factors of the potentiation of warfarin by clindamycin.

Recommendation

Following the assessment of the cumulative review submitted by the Marketing Authorisation Holder (MAH), the Pharmacovigilance Risk Assessment Committee (PRAC) agreed that the presented information is suggestive of a causal relationship between the administration of clindamycin and an increase in INR in patients maintained on vitamin K antagonists such as warfarin, acenocoumarol and fluindione. This includes three published literature reports in addition to spontaneous data. Two potential mechanisms have been proposed, with an effect on gut flora synthesis and absorption of vitamin K likely to have a greater impact than any pharmacokinetic interaction with metabolism of R-warfarin. Therefore, the PRAC recommended that the MAHs of the products containing clindamycin should submit a variation within 2 months to the National Competent Authority (NCA) to update the Product Information (PI) and include the following information below (new wording underlined):

Changes to the Product Information

Summary of Product Characteristics:

Section 4.5 - Interaction with other medicinal products and other forms of interaction:

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

Package Leaflet:

Section 2: Before you take Clindamycin – Taking other medicines.

Warfarin or similar medicines – used to thin the blood. You may be more likely to have a bleed. Your doctor may need to take regular blood tests to check how well your blood can clot.