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Repackaging Dabigatran into Compliance Packs

Compliance Packs

With an ageing population there is increasing incidence of multimorbidity and polypharmacy. This leads to complex dosing regimens.

Compliance aids, such as the Medico Paks® or unit dose medication sachets, are widely used to manage complex medication regimes, and help remind patients when to take medications (avoiding missed doses) or that a dose has been taken (avoiding overdosing). However, not all medications can be included in compliance packs.

Dabigatran

Dabigatran has an elimination half-life of 14 hours and is typically given twice daily for atrial fibrillation and treatment of venous thromboembolism. Data modelling has demonstrated that at steady state, even with the occasional doubled dose or missed dose, dabigatran concentrations remain within the desired therapeutic range, possibly negating the advantages of compliance aids. However, as patients taking dabigatran usually take multiple medications, packing all medications, including dabigatran, into a single compliance aid will help ensure adherence to the prescribed medication regimen.

Pradaxa® Formulation

Pradaxa® is the funded brand of dabigatran in New Zealand. The capsules contain multi-layered pellets consisting of a tartaric acid core coated with dabigatran etexilate. The tartaric acid core allows drug dissolution and promotes absorption. Following absorption dabigatran etexilate is rapidly converted to dabigatran (active form). In the presence of moisture the tartaric acid core of the pellets degrades and may affect absorption of dabigatran etexilate.

The manufacturer ensures the capsules are protected from moisture by packaging the capsules in sealed blister packs, and advises that the capsules should only be removed from the blister immediately before a scheduled dose. This poses a question, can dabigatran etexilate capsules be repackaged into compliance aids?

Stability of repackaged dabigatran etexilate

Higher temperature and moisture will accelerate the rate of degradation of dabigatran etexilate, but the issue is by how much. The rate of degradation after the repackaging the capsules into moisture impervious compliance aids has been examined in several studies [1-3]. These studies have used a variety of compliance aids each with similar physical properties to either Medico Paks® or to unit dose medication sachets. These studies found repackaged dabigatran etexilate capsules to be stable for at least 14 days, but there were conflicting results for longer storage periods.

When dabigatran etexilate capsules were repackaged into packaging similar to Medico Paks® and stored at high temperatures (30 °C) and high humidity (75 % relative humidity) this resulted in faster degradation. The dabigatran etexilate capsules remained within specification (90-110 %) for 14 days, but fell to 72 % by 28 days[1]. However, another study showed minimal degradation of dabigatran etexilate when stored in packaging similar to Medico Paks® or plastic unit dose packaging and stored at or below 25 °C (more consistent with New Zealand temperatures) for up to 120 days[2]. Neither study reported the temperature or humidity at the time of repackaging.

Premarketing stability studies demonstrated dabigatran etexilate capsules when stored in aluminium blister foils meet specification after 36 months stored at 25 °C/ 60 % relative humidity and at 30 °C/75 % relative humidity, and for 6 months at 40 °C/70 % relative humidity[3].

These studies support the repackaging of dabigatran etexilate into both 7 day and 28 day Medico Paks®, if stored at or below 25 °C, especially in patients for whom the benefits of compliance packaging are likely to outweigh any risks. We recommend storing in a cool place away from direct sunlight. At high temperature or humidity (e.g. patients travelling to tropical climates) the shelf life of Medico Paks® containing dabigatran etexilate should either be limited to a 14 days, or Medico Paks® should be stored in a refrigerator if a longer shelf life is required.

References

1. Robertson SG et al, Eur J Hosp Pharm 2017;0:1-5.doi:10.1136/ejhpharm-2017-001224
2. Wang EHZ et al, Can J Hosp Pharm 2015;68(1):16-21
3. CHMP Assessment Report for Pradaxa. Procedure No. EMEA/H/C/829. European Medicines Agency. EMEA/174363/2008