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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

27 Sep 2022

Dear Healthcare Professionals,

Methylphenidate long-acting (modified-release) preparations: caution if switching between products due to differences in formulations

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that prescribers and dispensers should use caution if switching patients between different long-acting formulations of methylphenidate (Concerta XL, Medikinet XL, Equasym XL, Ritalin LA, and generics) as different instructions for use and different release profiles may affect symptom management.

A recent European procedure looked at differences between Medikinet XL and other long-acting formulations of methylphenidate and the impact on safety and efficacy when switching to and from products. This procedure concluded that caution is advised if long-acting formulations of methylphenidate are used interchangeably due to the differences between formulations in frequency of dosing, administration with food, and plasma drug concentration achieved. These updates will be made to the United Kingdom Summary of Product Characteristics for Medikinet XL. MHRA has considered this, together with the safety data for all long-acting methylphenidate medicines, and agree with this position. MHRA also considered reports and queries from patients, carers and healthcare professionals in the United Kingdom regarding concerns of lack of effect and increased adverse effects when switching between long-acting formulations of methylphenidate. MHRA sought the views of the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines on these concerns.

MHRA is alerting healthcare professionals to the need to use caution when prescribing or dispensing long-acting methylphenidate preparations and to adequately counsel patients as required. MHRA will continue to monitor safety information and will seek to introduce this wording in other long-acting methylphenidate formulations as appropriate.

All long-acting methylphenidate preparations include an immediate-release component as well as a

modified-release component. This means methylphenidate is released in two phases (biphasic). This allows for rapid onset of action and a slower extended release, avoiding the need to take further doses during the day to maintain effect. It is possible that several formulations will need to be tried before one is found that suits an individual. The biphasic-release profiles of these products are not all equivalent and contain different proportions of the immediate-release and modified-release components. The differing time–action profiles provided by long-acting formulations of methylphenidate allow clinicians to target specific periods of the day that are particularly relevant for a patient, facilitating individualisation of attention deficit hyperactivity disorder (ADHD) treatment. Transferring to another formulation can result in changes in symptom management at key time periods during the day.

The response to methylphenidate varies greatly from patient to patient and therefore the doctor will need to increase or decrease a dose to find one that suits the patient (dose-finding phase). A number of long-acting methylphenidate preparations are available, and they differ from each other in several aspects, including: their available dose strengths; the ratio of immediate-release and modified-release methylphenidate; mechanism of release; pharmacokinetics; plasma concentration-time profiles and bioavailability; their dependence on the presence or absence of food at the time of ingestion. Due to these differences, changing preparations means that the dose may have to be adjusted to avoid the potential for overdose or underdose.

Switching between different preparations may result in concerns from patients and parents or caregivers. No single formulation meets the requirements of all patients with ADHD and the unique characteristics of each agent should be matched to the individual needs of the patient. Switching between formulations with differing pharmacokinetics can also be associated with differences in adverse events or patient experiences of effectiveness in both paediatric and adult patient groups. Frequent switching between different products should be avoided. Once a patient is established on a product, prescribers may wish to maintain them on that specific product. In such cases, prescribing by specifying brand or manufacturer may be appropriate. Changes to medication should only be made in the context of individual review and should be communicated to patients, who should be advised to report any changes to their symptoms or development of side effects.

Advice to healthcare professionals:

- Caution should be used if long-acting formulations of methylphenidate are to be used interchangeably due to the differences between formulations in dosing frequency, administration with food, amount and timing of the modified-release component, and overall clinical effect.
- Follow specific dosage recommendations for each formulation.
- If considering a switch to another long-acting preparation: consult with the patient (and their parent or caregiver if relevant) to discuss the reasons for this and the possible changes they may experience in symptom management and side effects (and what to do if these occur); consider

patient preferences such as their individual needs, dose frequency, possible side effects, or other issues related to the patient's condition; reiterate the instructions for use for the newly prescribed formulation, especially whether it should be taken with or without food.

- Clinical guidance advises to prescribe these long-acting formulations of methylphenidate by specifying brand name or by using the generic drug name and name of the manufacturer.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/methylphenidate-long-acting-modified-release-preparations-caution-if-switching-between-products-due-to-differences-in-formulations

In Hong Kong, there are 26 registered pharmaceutical products containing methylphenidate. Nineteen of them are modified-release preparations, including Medikinet CR Modified-release Capsules 40mg (HK-65756), Medikinet CR Modified-release Capsules 10mg (HK-65757), Medikinet CR Modified-release Capsules 20mg (HK-65758) and Medikinet CR Modified-release Capsules 30mg (HK-65759). All products are prescription-only medicines. So far, the Department of Health (DH) has received 2 cases of adverse drug reaction related to methylphenidate, but these cases were not related to switching between different preparations. In light of the above MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

pp (Terence MAN)
for Assistant Director (Drug)