Dear Healthcare Professionals,

**Insulins (all types): risk of cutaneous amyloidosis at injection site**

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency’s (MHRA) announcement that cutaneous amyloidosis at the injection site has been reported in patients using insulin and this may affect glycaemic control.

A recent European review of reports of insulin-derived cutaneous amyloidosis at insulin injection sites concluded that there is a clear causal relationship between cutaneous amyloidosis and all insulins and insulin-containing products. The Summaries of Product Characteristics and Patient Information Leaflets for all insulins and insulin-containing products are being updated to include this risk. Advice will also make clear the importance of site rotation and careful blood glucose monitoring following change of injection site to an unaffected area.

Insulin-derived amyloidosis is a specific form of localised cutaneous amyloidosis composed of insulin fibrils. It is likely caused by insulin accumulation at the injection sites, especially if these sites are used for repeated subcutaneous injections.

The European review considered cases of insulin-derived cutaneous amyloidosis reported in patients treated with all types of insulin. Some were identified by either histological examination, computerised tomography, or a combination of these. Presence of insulin in the amyloid was recognised by immunohistochemical analysis and in a single case further validated by mass spectrometry. In many of the cases initially analysed of the review, this resulted in poor glycaemic control (hyperglycaemia and hypoglycaemia).

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The evidence showed in many cases patients were routinely injecting into the same sites repeatedly rather than rotating injection sites. When outcome of glycaemic control was reported, most patients recovered after they began to use a proper site-rotation technique.

In the United Kingdom, up until the end of Jul 2019, 2 reports of cutaneous amyloidosis in patients receiving insulin therapy have been received via the MHRA’s Yellow Card Scheme. The European review was not able to estimate the frequency of cutaneous amyloidosis in patients using insulin from the data available, but reports have been received only very rarely. The literature suggests that cases of cutaneous amyloidosis may be under-reported and misdiagnosed as lipohypertrophy (a common increase in fat cells due to growth factor effect of insulin). Both conditions are characterised by lumps in the skin. However, where lipohypertrophy lesions are lobular and regress after stopping insulin injection, amyloid lesions are more solid and firm, do not regress quickly, and usually require surgical excision to treat.

While amyloid lesions can delay insulin absorption and affect glycaemic control if used as a site for administration, the skin changes are thought to be localised. Although some cases of cutaneous amyloidosis were reported as of a serious nature, they were mostly reported as such due to hospital admission to resect amyloid lesion. Aside from impact on glycaemic control, no other complications have been recognised.

Patients who inject insulin at the same site regularly are at an increased risk of developing cutaneous amyloidosis at the injection site and consequently may have poor diabetes control due to lack of insulin absorption due to the amyloid mass. To prevent or reduce this, patients should be advised to rotate injection sites within the same body region. There is a risk of hypoglycaemia in patients that suddenly change injection site from an area with cutaneous amyloidosis to an unaffected area (for example, changing the injection site from the torso to the leg). Patients should therefore carefully monitor blood glucose after changing injection site and consider adjusting the dose of insulin or antidiabetic medication to avoid hypoglycaemia, as needed.

Advice for healthcare professionals:
- Injection of insulin (all types) can lead to deposits of amyloid protein under the skin (cutaneous amyloidosis) at the injection site.
- Cutaneous amyloidosis interferes with insulin absorption, and administration of insulin at an affected site can affect glycaemic control.
- Remind patients to rotate injection sites within the same body region to reduce or prevent the risk of cutaneous amyloidosis and other skin reactions (for example, lipodystrophy).
- Consider cutaneous amyloidosis as a differential diagnosis to lipodystrophy when a patient presents with subcutaneous lumps at an insulin injection site.
- Advise patients that insulin may not work very well if they inject into an affected ‘lumpy’ area;

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to contact their doctor if they are currently injecting insulin into a ‘lumpy’ area before changing injection site since a sudden change may result in hypoglycaemia; to monitor carefully blood glucose after a change in injection site and that dose adjustment of insulin or other antidiabetic medication may be needed.

Please refer to the following website in MHRA for details:


In Hong Kong, there are 54 registered pharmaceutical products containing insulin. These products are drugs under supervised sales or prescription-only medicines. So far, the Department of Health (DH) has received 85 cases of adverse drug reaction related to insulin, but these cases are not related to cutaneous amyloidosis. In light of the above MHRA’s announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. 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 Undesirable Medical Advertisements and 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,

(Joseph LEE)
for Assistant Director (Drug)

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