Sultanate of Oman
Ministry of Health
Directorate General of Pharmaceutical Affairs
and Drug Control
MUSCAT

سلطنة عمان
وزارة الصحة
المديرية العامة للصيدلة
والرقابة الدوائية
مسقط

To:
THE DIRECTOR GENERAL OF HEALTH SERVICES IN ALL GOVERNORATES
Commanding Officer, Armed Forces Hospital (Al Khoudh & Salalah)
Director General of Royal Hospital
Director General of Khoula Hospital
Director General of Medical Supplies (MOH)
Director General of Pvt. Health Est. Affairs (to kindly arrange distribution to all Pvt. Hospitals)
Director General of Primary Health Care, MOH
Director General of Specialised Medical Care, MOH
Director General of Quality Assurance Centre, MOH
Director of Rational Drug Use
Hospital Director (Al Nahda Hospital)
Hospital Director (Al Massara Hospital)
The Head of Medical Services in SQU Hospital
The Head of Medical Services in Royal Oman Police
The Head of Medical Services in Ministry of Defence
The Head of Medical Services in The Diwan
The Head of Medical Services in The Sultan's Special Force
The Head of Medical Services in Internal Security Services
The Head of Medical Services in Petroleum Development of Oman
The Head of Medical Services in LNG Oman
ALL PRIVATE PHARMACIES & DRUG STORES

After Compliments,

Please find attached our Circular No. 222 dated 29/11/20 regarding drug safety update from MHRA about Ferric carboxymaltose (Ferinject): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures.

Copy to:

- Director, Office of H.E. The Undersecretary for Health Affairs
- Director of Pharmacovigilance & Drug Information Dept, DGPA&DC
- Director of Medical Device Control, DGPA&DC
- Director of Drug Control Department, DGPA&DC
- Director of Pharmaceutical Licensing Department, DGPA&DC
- Director of Central Quality Control Lab., DGPA&DC
- Supdt. of Central Drug Information

ص . ب: ٣٩٣ مسقط - الرمز البريدي: ١٠٠ - هاتف: ٢٢٣٥٧١١١ - فاكس: ٢٢٣٥٨٤٨٩ البريد الإلكتروني : dg-padc@moh.gov.om
P.O. Box : 393 Muscat, Postal Code: 100, Tel: 22357111 - Fax: 22358489 - E-mail : dg-padc@moh.gov.om

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Circular No. 222 **/ 2020**

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29 -11-2020

Ferric carboxymaltose (Ferinject): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures

The Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom has recently posted in their website an important drug safety update about Ferric Carboxymaltose and risk of symptomatic hypophosphataemia leading to osteomalacia and fractures.

Ferric carboxymaltose is indicated for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used and there is a clinical need to deliver iron rapidly. Ferinject has been associated with common cases of hypophosphatemia (low blood phosphate).

A recent European review concluded that ferric carboxymaltose is associated with hypophosphataemic osteomalacia (inadequate mineralisation of the bone matrix leading to softening of the bones). The review recommended strengthened advice to make healthcare professionals aware that osteomalacia can be a consequence of hypophosphataemia and to ensure early detection and effective management of hypophosphataemic osteomalacia.

Based on the available data, it is difficult to estimate the magnitude of the risk of hypophosphataemic osteomalacia with ferric carboxymaltose, therefore the risk of this adverse reaction is included in the product information with a frequency category of not known.

Cases of osteomalacia in post-marketing use

As per the information posted by MHRA, as of 14 February 2020, the review considered 36 spontaneous cases worldwide in patients with concurrent hypophosphataemia associated with ferric carboxymaltose. Osteomalacia was reported in 28 cases and hypophosphataemic osteomalacia in 6 cases, with 2 cases reporting both terms. As of February 2020, the worldwide estimated exposure to ferric carboxymaltose was estimated to be 12,491,000 patient-years (168,632,771 defined daily doses).

In most cases (30 [83%]) hypophosphataemia was reported as medically significant (moderate to severe) using a phosphate cut-off of lower than 2.0 milligram per decilitre.

Where reported the patient age was 26–39 years in 8 cases, 40–56 years in 12 cases, 57–68 years in 4 cases, and 73–81 years in 3 cases.

Where dosing information was reported, 13 patients had been given doses of 1000mg per infusion of ferric carboxymaltose for an average of 19 infusions over a period of 5–24 months. The time to onset of osteomalacia after starting treatment with ferric carboxymaltose at 1000mg dose was reported in 6 cases and ranged from 3 months to 5 years (median 14.5 months).

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ص . ب: ٣٩٣ مسقط - الرمز البريدي: ١٠٠ - هاتف: ٢٢٣٥٧١١١ - فاكس: ٢٢٣٥٨٤٨٩ البريد الإلكتروني : dg-padc@moh.gov.om
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Of the 36 cases, 24 cases reported one or more reliable diagnostic criteria for osteomalacia: alkaline phosphatase (12 cases), parathyroid hormone (12 cases), magnetic resonance imagery (11 cases), bone scan (5 cases), bone biopsy (3 cases), and bone densitometry (2 cases).

All 36 cases presented with one or more risk factors for osteomalacia, namely inflammatory bowel disease (14 cases), vitamin D deficiency (9 cases), osteoporosis (8 cases), malabsorption (6 cases), Rendu-Osler disease (6 cases), hyperparathyroidism (6 cases), long-term steroid use (6 cases), and chronic use of antacid therapies (3 cases).

Approximately half of the patients (19 of 36; 53%) developed one or more fractures (where reported, femoral neck fracture or pelvic or hip fracture) in conjunction with osteomalacia.

Where reported, the outcome for the patient was recovered in 7 cases and recovering in 9 cases. The patients were treated with phosphate, calcium and/or vitamin D supplements. Where required, surgical treatment was provided for fractures.

In the UK up to 22 October 2020, received 28 Yellow Card reports of hypophosphataemia and 2 reporting cases of hypophosphataemic osteomalacia with Ferinject. These UK cases were considered as part of the EU review.

Advice for healthcare professionals:

- Ferric carboxymaltose is known to be commonly associated with hypophosphatemia
- cases have been reported of symptomatic hypophosphataemia leading to infrequent reports of hypophosphataemic osteomalacia and fractures in patients with existing risk factors and following prolonged exposure to high doses – some cases required clinical intervention, including surgery
- monitor serum phosphate levels in patients:
  - requiring multiple administrations of ferric carboxymaltose at higher doses
  - on long-term treatment with ferric carboxymaltose
  - with pre-existing risk factors for hypophosphataemia such as vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, inflammatory bowel disease, and osteoporosis
- advise patients to seek medical advice if they experience symptoms indicative of hypophosphataemia, including new musculoskeletal symptoms or worsening of tiredness – be aware these symptoms may be confused with those of iron deficiency anaemia
- if hypophosphataemia persists, re-evaluate treatment with ferric carboxymaltose

Call to Report Suspected Adverse Drug Reactions

The product Ferinject is registered in Oman. Healthcare professionals are encouraged to report any adverse events suspected to be associated with the above product or any other medicinal product to the Department of Pharmacovigilance & Drug Information in DGPA&DC. The submission to be done electronically through the MOH e-portal.

Dr. Mohammed Hamdan Al Rubaie
Director General