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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.)

30 Nov 2022

Dear Healthcare Professionals,

Dupilumab (Dupixent▼): risk of ocular adverse reactions and need for prompt management

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that healthcare professionals prescribing dupilumab should be alert to the risk of ocular adverse reactions and need for prompt management.

The potential for adverse reactions affecting the eye with dupilumab was established in the initial clinical trials. Further ocular adverse reactions have been identified during post-marketing clinical use. Although most ocular reactions are mild, some can become serious. MHRA has received a small number of Yellow Card reports of ulcerative keratitis with serious corneal damage associated with dupilumab treatment. MHRA recently reviewed the risk of dry eye and also serious ocular side effects associated with dupilumab. The review recommended that updates should be made to the product information for dupilumab to include the adverse drug reaction 'dry eye' and also to emphasise the need for prompt and appropriate management of any potential ocular reactions. It is not currently possible to predict who may experience the rarer and most serious ocular adverse reactions, such as ulcerative keratitis. It is therefore important, with all ocular reactions, for patients to receive prompt care, with treatment provided as appropriate to prevent or minimise damage to the eye.

MHRA is also alerting healthcare professionals prescribing tralokinumab. Clinical trial data have indicated that keratitis, conjunctivitis and allergic conjunctivitis are associated with tralokinumab use. MHRA is advising healthcare professionals prescribing dupilumab and tralokinumab to discuss with patients the potential for side effects affecting the eye and to ensure any reactions are managed promptly, especially in a patient experiencing eye pain or changes to their vision.

Up to 7 Sep 2022, MHRA has received 479 reports in the United Kingdom which included suspected ocular side effects with dupilumab. 111 of these reports were considered serious. 9 reports of ulcerative

keratitis were received, representing 5 cases (for some individual cases, MHRA received more than one report from different sources). 2 of these cases involved corneal perforation. 18 reports involved children ranging from 6 to 17 years of age. With regards to the ocular events listed for dupilumab, please refer to the website in MHRA for details of the number of reports in the United Kingdom received by MHRA. Up to 7 Sep 2022, MHRA has received no ocular related reports regarding tralokinumab.

Patients with atopic dermatitis commonly present with ocular surface diseases such as allergic conjunctivitis, blepharitis, and keratitis, as well as infectious conjunctivitis and keratoconus (changes to the shape of the cornea). The mechanisms by which dupilumab or tralokinumab increase the occurrence of, or exacerbate, ocular adverse events are not fully understood. Publications, including individual case reports about patients experiencing suspected ocular side effects with dupilumab, show variability in timing of onset and progression, presentation, and sequelae of ocular adverse reactions. In most reports received by MHRA where patients have experienced ocular adverse reactions with dupilumab, the reactions have not been considered to be serious by the reporter. However, MHRA has received 9 reports of 5 patients who experienced ulcerative keratitis with dupilumab, and, where the information was provided, treatment required corneal gluing or tectonic keratoplasty. The details of some of the serious reports, and expert advice, indicate that early review and intervention are beneficial to the patient.

Expert ophthalmology and dermatology advice provided to MHRA indicated that in clinical experience in the United Kingdom, most ocular reactions seen with dupilumab are mild and can be managed. However, it is not currently possible to predict who may experience the rarer and most severe ocular adverse reactions, such as ulcerative keratitis. It is therefore important, with all ocular reactions, for patients to receive prompt care, with treatment provided as appropriate to prevent or minimise damage to the eye. It is important to recognise 'red flags' for urgent ophthalmological consultation, such as eye pain, vision loss, and an increase in ocular pressure.

Advice for healthcare professionals:

- Dupilumab is commonly associated with cases of conjunctivitis and allergic conjunctivitis, eye pruritus, blepharitis, and dry eye and with infrequent cases of keratitis and ulcerative keratitis, especially in patients with atopic dermatitis.
- Be alert to the risks of ocular reactions and promptly review new onset or worsening ocular symptoms, referring patients for ophthalmological examination as appropriate. Sudden changes in vision or significant eye pain that does not settle warrant urgent review.
- Discuss with patients or caregivers the potential for, and symptoms of, ocular side effects at initiation of dupilumab, including symptoms of conjunctivitis and dry eye (which can also include paradoxical eye watering), keratitis and ulcerative keratitis.
- Advise patients to promptly report new-onset or worsening eye symptoms to their healthcare professional so that appropriate treatment can be initiated. Advise patients not to self-manage

ocular symptoms.

- Ensure that patients who develop conjunctivitis or dry eye that does not resolve following initial treatment, or patients with signs and symptoms suggestive of keratitis (especially eye pain and vision changes), undergo ophthalmological examination, as appropriate.
- MHRA reminds healthcare professionals that tralokinumab (Adtralza▼), another interleukin-13 inhibitor recently licenced for use in atopic dermatitis, is also associated with common cases of conjunctivitis and allergic conjunctivitis as well as uncommon cases of keratitis, and that patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/dupilumab-dupixentv-risk-of-ocular-adverse-reactions-and-need-for-prompt-management

In Hong Kong, there are 2 registered pharmaceutical products containing dupilumab, namely Dupixent Solution For Injection In Pre-filled Syringe 300mg/2ml (HK-65961) and Dupixent Solution For Injection In Pre-filled Syringe 200mg/1.14ml (HK-66635). Both products are registered by Sanofi Hong Kong Limited. They are prescription-only medicines. There is no registered pharmaceutical product containing tralokinumab. So far, the Department of Health (DH) has received 8 cases of adverse drug reaction related to dupilumab, of which one case was related to vision abnormal and one case was related to corneal ulcer. 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,

(Terence MAN)
for Assistant Director (Drug)