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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.)

DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG INFORMATION AND
PHARMACOVIGILANCE DIVISION
Suites 2002-05, 20/F, AIA Kowloon Tower,
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19 Jan 2022

Dear Healthcare Professionals,

Brolucizumab (Beovu▼): risk of intraocular inflammation and retinal vascular occlusion increased with short dosing intervals

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that maintenance doses of brolucizumab (after the first 3 doses) should not be given at intervals of less than 8 weeks apart.

Intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions known to be associated with brolucizumab. New information on these adverse events, including risk factors and possible mechanism, was considered in a recent European safety review. The product information of brolucizumab will also be updated to reflect this information.

Preliminary results were recently received from the MERLIN study. This is a 2-year United States multicentre, randomised, double-masked phase 3A study to assess the safety and efficacy of the recommended dose of brolucizumab (6mg), administered every 4 weeks, compared to aflibercept 2mg every 4 weeks, in patients with neovascular (wet) age-related macular degeneration (AMD) with persistent retinal fluid. In MERLIN, intraocular inflammation, including retinal vasculitis, were reported with a higher frequency in the group receiving brolucizumab 6mg every 4 weeks compared with those receiving aflibercept 2mg every 4 weeks (9.3% versus 4.5%, respectively). Frequency of retinal vascular occlusion was also higher with brolucizumab (2.0% versus 0%, respectively). In addition, the incidence of intraocular inflammation with 4-weekly dosing of brolucizumab in MERLIN (9.3%) was of a higher frequency than that recorded in the pivotal phase 3 clinical studies using a brolucizumab dosing interval of 6mg every 8 weeks and 12 weeks (4.4%).

Two non-interventional retrospective studies (NCT05082415 and NCT05111743) of large United States real-world databases in patients with neovascular AMD aimed to better understand the incidence of these adverse events up to 6 months after initiating treatment with brolucizumab. The results of these

studies suggest that patients with a medical history of intraocular inflammation or retinal vascular occlusion in the year before treatment with brolucizumab are more likely to present with similar events after brolucizumab injection, as compared with patients with neovascular AMD with no history of these events. In addition, a higher risk of intraocular inflammation (including retinal vasculitis and retinal vascular occlusion) in female patients was observed both in the two retrospective studies and also in the clinical trials (5.3% of female patients and 3.2% of male patients in the pivotal clinical trials). A higher incidence of these events was also seen in patients of Japanese ancestry than in those of non-Japanese ancestry.

The review also considered new data to elucidate the mechanism of these adverse events. As brolucizumab is a therapeutic protein, there is a potential for immunogenicity and consequently intraocular inflammation. Evidence to support this mechanism comes from a study in 5 patients with neovascular AMD injected with brolucizumab who subsequently developed retinal vasculitis or retinal vascular occlusion. Blood samples from these 5 patients identified a humoral and cellular immune response against brolucizumab 3 to 5 months after the last brolucizumab dose. In samples from 6 control patients who had no signs or symptoms of intraocular inflammation while receiving brolucizumab, anti-drug antibodies, when present, had lower titres.

Advice for healthcare professionals:

- Intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions uncommonly associated with intravitreal injection of brolucizumab.
- In patients who develop intraocular inflammation or retinal vascular occlusion, discontinue treatment with brolucizumab and manage events promptly.
- To reduce the risk of these events, do not administer maintenance doses of brolucizumab (after the first 3 doses) at intervals of less than 8 weeks apart.
- Closely monitor patients treated with brolucizumab who have a medical history of intraocular inflammation or retinal vascular occlusion (within 12 months before the first brolucizumab injection) since they are at increased risk of developing these adverse reactions post-injection.
- Intraocular inflammation or retinal vascular occlusion may occur at any time during brolucizumab treatment but occur more frequently during early treatment.
- Based on observational studies, retinal vasculitis and retinal vascular occlusion after brolucizumab treatment appear to be more frequent in female patients and in patients of Japanese ancestry.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/brolucizumab-beovuv-risk-of-intraocular-inflammation-and-retinal-vascular-occlusion-increased-with-short-dosing-intervals

In Hong Kong, there are 2 registered pharmaceutical products containing brolucizumab, namely Beovu Solution For Injection 6mg/0.05ml (HK-67008) and Beovu Solution for Injection In Pre-filled Syringe 6mg/0.05ml (HK-67009). Both products are registered by Novartis Pharmaceuticals (HK) Limited. They are prescription-only medicines. So far, the Department of Health (DH) has received 9 cases of adverse drug reaction related to brolucizumab, of which one case was related to retinal vasculitis and another case was related to retinal vasculitis and retinal vein occlusion. 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)