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NEGARA BRUNEI DARUSSALAM

Ref: (23)DGMHS/5/2018/B Pt.6

16th July 2024

Dear Product Licence Holders and Importers,

**DIRECTIVE ON THE CONTROL OF NITROSAMINE AND / OR AZIDO IMPURITIES IN MEDICINAL PRODUCTS**

Following the detection of harmful levels of the nitrosamine impurity, N-nitrosodimethylamine (NDMA) in Angiotensin-II Receptor Blockers (ARBs) in 2018, further nitrosamine impurities which are potentially carcinogenic have been detected in several other medicinal products in subsequent years through our pharmacovigilance activities. With this emerging safety concern, the Brunei Darussalam Medicines Control Authority (BDMCA) had previously issued directives on the importation and sale of ARBs, Metformin, Amitriptyline, Ranitidine and Varenicline in 2019 and 2021 to all Product Licence Holders and importers to undertake risk assessment and provide supporting documents such as Certificate of Analysis (COA) of Finished Products and Active Pharmaceutical Ingredient corresponding to the batch imported into Brunei Darussalam and level of nitrosamine and / or azido impurities for every consignment imported into Brunei Darussalam.

2. As part of our continuous effort in monitoring the current developments on the control of nitrosamine impurities in medicinal products, the BDMCA in its 47th Meeting held on 22nd June 2024 has reviewed the requirements for registration, importation and sale of ARBs, Metformin, Amitriptyline, Ranitidine and Varenicline containing products in Brunei Darussalam. This update is in line with the approach by other national regulatory authorities such as US FDA and EMA.

3. This directive now supersedes the following directives:

a) Importation and Sale of Ranitidine Products in Brunei Darussalam, ref: (202) DPS/ADMIN/2018 dated 15 October 2019
b) Importation and Sale of Metformin Products in Brunei Darussalam, ref: (230) DPS/ADMIN/2018 dated 11 December 2019
c) Importation and Sale of Amitriptyline Products in Brunei Darussalam, ref: (03) PRS/ADMIN/2021 dated 12 August 2021
d) Importation and Sale of Angiotensin-II Receptor Blockers (ARBs) in Brunei Darussalam, ref: (08) PRS/ADMIN/2021 dated 4 December 2021
e) Importation and Sale of Varenicline Products in Brunei Darussalam, ref: (09) PRS/ADMIN/2021 dated 4 December 2021.

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4. As the manufacturer has the responsibility in ensuring the quality, safety and effectiveness of the product throughout its lifecycle, prospective measures and a control strategy should be in place to minimize the risk of generation / contamination with any nitrosamine. This includes but is not limited to performing risk assessment, confirmatory testing if required and risk mitigation of their products.

5. All Product Licence Holders and Importers are therefore required to comply with the following requirements:

   a) Registered Medicinal Products

      i. The Product Licence Holder is required to ensure the specification for nitrosamines and / or azido impurities are registered. Submission of supporting documents for risk assessment such as COA and nitrosamine impurity level for every batch imported into Brunei Darussalam shall no longer be required provided that the incoming stocks carry the updated specifications for nitrosamines and / or azido impurities.

      ii. Variation submission for change in specification to include nitrosamines and / or azido impurities is required if these impurities have not been registered. The current procedure of submission of supporting documents for risk assessment which appears as **ANNEX A** for every batch imported into Brunei Darussalam shall still be required until the variation application has been approved by the Drug Registration Committee (DRC) and the incoming stocks carry the updated specifications for nitrosamines and / or azido impurities.

      iii. For incoming stocks which carry the previous specifications (without nitrosamines and / or azido impurities), the Product Licence Holder shall still be required to submit the supporting documents for risk assessment which appears as **ANNEX A** for every batch imported into Brunei Darussalam.

      iv. The Product Licence Holder shall be responsible in ensuring all marketed batches of the medicinal products imported into Brunei Darussalam are below the acceptable limit. Should there be any safety issue, the Product Licence Holder is required to provide necessary data / test results for the affected products.

      v. In the event that product is found to have nitrosamines and / or azido impurities above the acceptable level, the Product Licence Holder is required to inform the Authority on their proposed market action.

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b) Medicinal Products imported via Application for Import Permit of Medicinal Products with Special Approval (SMP)

i. The Import Licence Holder shall still be required to submit the supporting documents for risk assessment which appears as **ANNEX A** for every batch imported into Brunei Darussalam.

6. The above requirement shall be implemented with **immediate effect commencing 16th July 2024.**

7. Product Licence Holders and Importers may refer to the **Flowchart on the Control of Nitrosamine and / or Azido Impurities in Medicinal Products** which appears as **ANNEX B** as a guidance.

8. The BDMCA shall continue to work closely with other national regulatory authorities to verify that appropriate actions are taken to minimize or avoid the presence of nitrosamine impurities and to monitor the content of nitrosamine impurities in medicinal products and ensure the safety, quality and efficacy of these products are not compromised.

Your cooperation in the matter is highly appreciated.

Yours sincerely,

**Chair**
Brunei Darussalam Medicines Control Authority
Ministry of Health
Brunei Darussalam