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Tarikh : 07 Disember 2020

SEMUA PEMEGANG PENDAFTARAN PRODUK

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan/ Puan

PEKELILING BERKENAAN KEPERLUAN PENGUJIAN IMPURITI *NITROSAMINE* BAGI PRODUK YANG MENGANDUNGI *ANGIOTENSIN II RECEPTOR BLOCKERS* (ARB), RANITIDINE DAN METFORMIN

Adalah saya merujuk kepada perkara di atas.

2. Susulan pengesanan *nitrosamine* dalam produk yang mengandungi *Angiotensin II Receptor Blockers* (ARB), Metformin dan Ranitidine di peringkat antarabangsa oleh badan-badan regulatori antarabangsa sejak Jun 2018, Bahagian Regulatori Farmasi Negara (NPRA) telah mengambil beberapa langkah regulatori bagi menangani isu ini seperti berikut:

2.1 Mengeluarkan beberapa surat arahan kepada pemegang pendaftaran produk yang terlibat sejak November 2018 berkaitan pengujian kandungan *nitrosamine* dalam produk-produk tersebut. Dalam surat arahan yang sama, pemegang pendaftaran diingatkan supaya memastikan semua kelompok baharu yang akan dipasarkan tidak mengandungi *nitrosamine* melebihi had yang ditetapkan.

2.2 Tindakan memanggil balik kelompok produk berdaftar yang dikesan mengandungi *nitrosamine* melebihi had yang ditetapkan.

3. Sebagai kesinambungan kepada tindakan-tindakan regulatori yang telah dilaksanakan dan selaras dengan panduan serta laporan yang dikeluarkan oleh *European Medicines Agency* (EMA) dan *U.S. Food and Drug Administration* (USFDA), semua pemegang pendaftaran produk dikehendaki memasukkan **ujian kandungan *nitrosamine*** sebagai ujian dalam spesifikasi (produk dan bahan aktif) untuk **permohonan pendaftaran produk baharu** dan **produk berdaftar** bagi produk yang mengandungi ***Angiotensin II Receptor Blockers* (ARB), Ranitidine dan Metformin.**

4. Maklumat berkaitan yang perlu dikemukakan melalui permohonan pendaftaran produk baharu atau permohonan variasi adalah seperti pada **Lampiran 1.**

5. Pelaksanaan keperluan ini adalah seperti berikut:

5.1 Permohonan Pendaftaran Produk Baharu

5.1.1 Peringkat pra-penilaian: **Serta merta**

5.1.2 Dalam proses penilaian: **Serta merta**

5.2 Produk Berdaftar:

Diberi tempoh sehingga **30 Jun 2021**

6. Pemegang pendaftaran juga perlu menilai semula risiko kehadiran *nitrosamine* apabila terdapat perubahan terhadap proses pengilangan, pengilang, kaedah penyimpanan, pembungkusan atau sebarang perubahan yang boleh menyebabkan risiko pembentukan atau kontaminasi *nitrosamine* bagi bahan aktif dan/ atau produk siap. Maklumat ini perlu dikemukakan dan dinilai oleh NPRA melalui permohonan variasi dari semasa ke semasa sepanjang produk berdaftar dan dipasarkan di Malaysia.

7. Pemegang pendaftaran bertanggungjawab untuk memastikan semua kelompok yang dipasarkan mematuhi had *nitrosamine* yang ditetapkan. NPRA sentiasa menjalankan pemantauan secara berkala terhadap produk-produk tersebut di pasaran bagi memastikan aspek kualiti, keselamatan dan keberkesanan produk dipatuhi.

8. Semua pemegang pendaftaran produk berkaitan dikehendaki mematuhi keperluan seperti yang dinyatakan.

Sekian, terima kasih

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah,

(DR HASENAH BINTI ALI) RPh. 1517
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Lampiran 1

INFORMATION REQUIRED ON THE CONTROL OF NITROSAMINES IMPURITIES

1. This requirement is applicable to products containing Angiotensin II Receptor Blockers (ARB), Metformin and Ranitidine

2. New Product Registration Application

2.1 Section S (Active Pharmaceutical Ingredient (API) Information)

No.	Field	Description
Part II S (API information)		
1.	S3.2 Impurities	Discussion on possible formation of nitrosamines impurities and the control strategy
2.	S4.1 Specification	(i) Routine testing of nitrosamines in API specification from API Manufacturer (ii) Routine testing of nitrosamines in API specification from Product Manufacturer **Note:** <u>Nitrosamine Limit[1]:</u> N-nitrosodimethylamine (NDMA): 96.0 ng/ day N-nitrosodiethylamine[2] (NDEA): 26.5 ng/ day [1] Limit/ Testing results should be expressed in ng and ppm (according to maximum daily dose). The limits are applicable only if an API contain a single nitrosamine. In the case when more than one nitrosamine is identified, the total nitrosamine limit should not exceed the limit of the most potent nitrosamine identified. [2] Only applicable to ARB <u>Skip Testing</u>: a. Skip testing is only justified if it can be shown that the levels of nitrosamine are consistently ≤ 30% of the limit defined above and the root cause is identified and well-understood. b. The testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. If fewer than 3 batches are manufactured annually, then all batches should be tested. Please refer to **S4.5** References: a. EMA: Procedure under Article 5(3) of Regulation EC (No) 726/2004 Nitrosamine impurities in human medicinal products, 25 June 2020 b. USFDA: Control of Nitrosamine Impurities in Human Drugs Guidance for Industry, 1 September 2020 c. The European Pharmacopoeia (Ph. Eur.)

Lampiran 1

No.	Field	Description
3.	S4.2 Analytical Procedures	Protocol of Analysis[#] (POA) for nitrosamine impurities (including results and raw data) from API manufacturer
4.	S4.3 Validation of Analytical Procedures	Analytical Method Validation[#] (AMV) for nitrosamine impurities test (including raw data) from API manufacturer
5.	S4.4 Batch Analysis	Batch Analysis Data for nitrosamines content in API (minimum 3 batches)
6.	S4.4.1 Certificate of Analysis (CoA)	(i) CoA of API from API Manufacturer (2 batches) (ii) CoA of API from Product Manufacturer (2 batches)
7.	S4.5 Justification of Specification	Justification for Skip Testing or Omission i. Skip testing is only justified if it can be shown that the levels of nitrosamine are consistently ≤ 30% of the limit defined above and the root cause is identified and well-understood. ii. Omission from the specification is only justified if it can be shown that the levels of nitrosamine are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood. iii. Relevant document to support skip testing or omission from specification should be included in S4.5. such as: a. Risk Assessment Summary Report Risk Assessment should cover all possible source of nitrosamines such as: • product or active ingredient manufacturing process, • chemical structure • the conditions in which the product/ APIs are stored or packaged. b. Test results from a minimum of 6 pilot scale batches or 3 production scale batches **Note:** Nitrosamine Limit: Refer to **S4.1** References: a. EMA: Procedure under Article 5(3) of Regulation EC (No) 726/2004 Nitrosamine impurities in human medicinal products, 25 June 2020 b. USFDA: Control of Nitrosamine Impurities in Human Drugs Guidance for Industry, 1 September 2020 c. The European Pharmacopoeia (Ph. Eur.)

[#] For the details on requirement of Protocol of Analysis and Analytical Method Validation, kindly refer to http://www.npra.gov.my

Lampiran 1

Note: For the API information submitted through CEP option, requirement for nitrosamine routine testing should be in line with Ph.Eur. monograph; and any additional tests and acceptance criteria stated in the CEP.

2.2 Section P (Drug Product Information)

No.	Field	Description
Part II P (Drug Product information)		
1.	P5.1 Specification	Routine testing of nitrosamines in product specification **Note:** <u>Nitrosamine Limit[1]:</u> N-nitrosodimethylamine (NDMA): 96.0 ng/ day N-nitrosodiethylamine[2] (NDEA): 26.5 ng/ day [1] Limit/ Testing results should be expressed in ng and ppm (according to maximum daily dose). The limits are applicable only if a finished product contains a single nitrosamine In the case when more than one nitrosamine is identified, the total nitrosamine limit should not exceed the limit of the most potent nitrosamine identified. [2] Only applicable to ARB <u>Skip Testing</u>: a. Skip testing is only justified if it can be shown that the levels of nitrosamine are consistently ≤ 30% of the limit defined above and the root cause is identified and well-understood. b. The testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. If fewer than 3 batches are manufactured annually, then all batches should be tested. Please refer to **P5.6** <u>References:</u> a. EMA: Procedure under Article 5(3) of Regulation EC (No) 726/2004 Nitrosamine impurities in human medicinal products, 25 June 2020 Control of Nitrosamine Impurities in Human Drugs Guidance for Industry b. USFDA: Control of Nitrosamine Impurities in Human Drugs Guidance for Industry, 1 September 2020 c. The European Pharmacopoeia (Ph. Eur.)
2.	P5.2 Analytical Protocol	Protocol of Analysis[#] (POA) for nitrosamine impurities (including results and raw data) from product manufacturer

Lampiran 1

No.	Field	Description
3.	P5.3 Validation of Analytical Protocol	Analytical Method Validation[#] (AMV) for nitrosamine impurities test (including raw data) from product manufacturer
4.	P5.4 Certificate of Analysis (CoA)	CoA of finished product (2 batches)
5.	P5.5 Characterisation of Impurities	Discussion on possible formation of nitrosamines impurities and the control strategy
6.	P5.6 Justification of Specification	<u>Justification for Skip Testing or Omission</u> i. Skip testing is only justified if it can be shown that the levels of nitrosamine are consistently ≤ 30% of the limit defined above and the root cause is identified and well-understood. ii. Omission from the specification is only justified if it can be shown that the levels of nitrosamine are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood. iii. Relevant document to support skip testing or omission from specification should be included in P5.6. such as: a. Risk Assessment Summary Report Risk Assessment should cover all possible source of nitrosamines such as: • product or active ingredient manufacturing process, • chemical structure • the conditions in which the product/ APIs are stored or packaged. b. Test results from a minimum of 6 pilot scale batches or 3 production scale batches **Note:** <u>Nitrosamine Limit:</u> Refer to **P5.1** <u>References:</u> a. EMA: Procedure under Article 5(3) of Regulation EC (No) 726/2004 Nitrosamine impurities in human medicinal products, 25 June 2020 b. USFDA: Control of Nitrosamine Impurities in Human Drugs Guidance for Industry, 1 September 2020 c. The European Pharmacopoeia (Ph. Eur.)

Lampiran 1

No.	Field	Description
7.	P8 Stability Data	i. To include the nitrosamine impurities test in on-going stability study if there is on-going stability study ii. To submit commitment letter on the inclusion of the nitrosamine impurities test during stability study of on-going batches/ new batches and the expected date in which the report can be submitted

[#] For the details on requirement of Protocol of Analysis and Analytical Method Validation, kindly refer to http://www.npra.gov.my

3. Variation Application

3.1 All product registration holder (PRH) shall **update** the routine testing of nitrosamine impurity in the product/ active ingredient specification **by 30th June 2021.**

The PRH shall also assess the risk of presence of nitrosamine impurities throughout the product lifecycle and make an **update** to the product/ active ingredient specification following **any future changes** related to product or active ingredient manufacturing process/ manufacturer, the conditions in which the products/ active ingredient are stored or packaged, or any other changes that may pose the risk of nitrosamine formation/ contamination.

The updated specification and related document shall be submitted through variation application as the following (where applicable):

3.2 Changes involving the Drug Substance/ Active Ingredient

The relevant variation types include:

No.	Variation Type	Description
1.	**MaV-3**	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
2.	**MaV-4**	Major change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
3.	**MaV-7**	Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available] a) Specification limits are widened and/or deletion of test parameter and limits of drug substance b) Specification limits are widened and/or deletion of test parameter and limits of drug product

Lampiran 1

No.	Variation Type	Description
4.	**MiV-PA5**	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
5.	**MiV-PA7**	Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
6.	**MiV-PA8**	Minor change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
7.	**MiV-PA9**	Change of the specification of drug substance a) Specification limits are tightened b) Addition of new test parameter and limits
8.	**MiV-PA10**	Change of the test procedure of non-compendial drug substance
9.	**MiV-PA13**	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
10.	**MiV-N10**	Change of specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium

* **Documents required are as stated in 2.1 above.**

3.3 Changes involving the Drug Product

The relevant variation types include:

No.	Variation Type	Description
1.	**MAV-7**	Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available] a) Specification limits are widened and/or deletion of test parameter and limits of drug substance b) Specification limits are widened and/or deletion of test parameter and limits of drug product
2.	**MaV-11**	Qualitative or quantitative change of excipient a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline) b) For modified release oral dosage forms c) For other critical dosage forms such as sterile preparations.

Lampiran 1

No.	Variation Type	Description
3.	**MaV-13**	Change in primary packaging material for sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material
4.	**MiV-PA16**	Qualitative and/or quantitative change of excipient a) For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline) b) For other non-critical dosage forms e.g. oral liquid, external preparation.
5.	**MiV-PA18**	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
6.	**MiV-PA25**	Change of release and shelf-life specifications of the drug product
7.	**MiV-PA28**	Change in the test procedure of the drug product (including replacement or addition of a test procedure)
8.	**MiV-PA29**	Change in primary packaging material for non-sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material
9.	**MiV-N10**	Change of specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium

*__Documents required are as stated in 2.2 above.__